British Journal of Diseases of the Chest

EDITOR
PHILIP ELLMAN
ASSISTANT EDITOR
J. R. BELCHER

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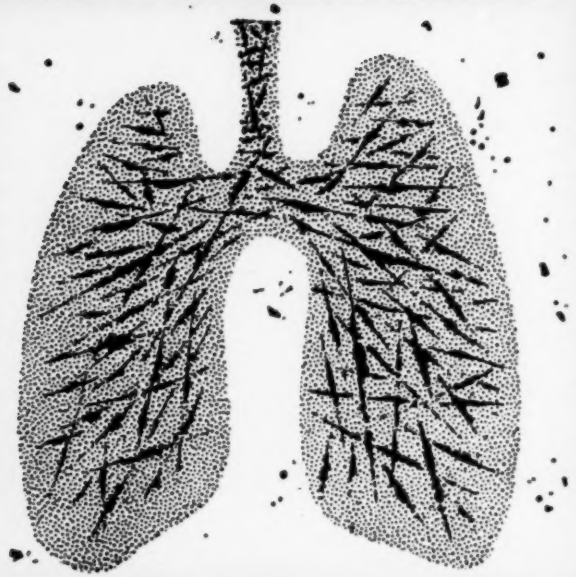

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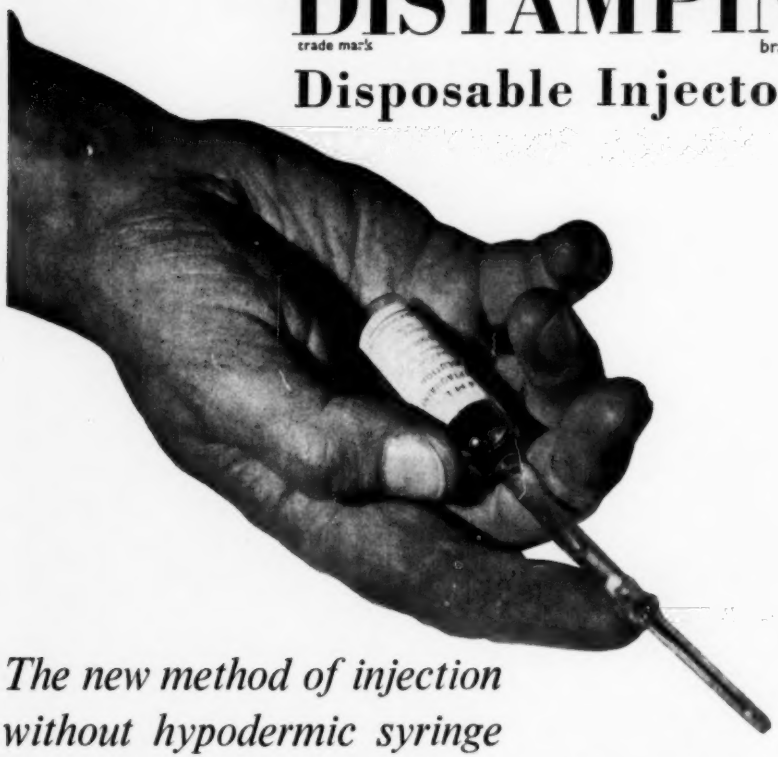

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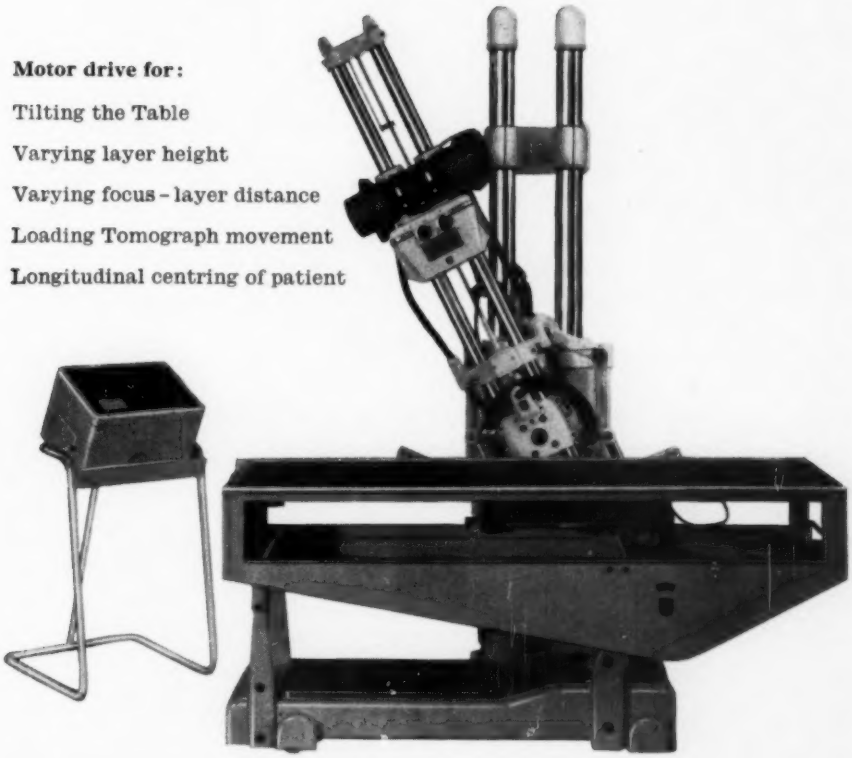

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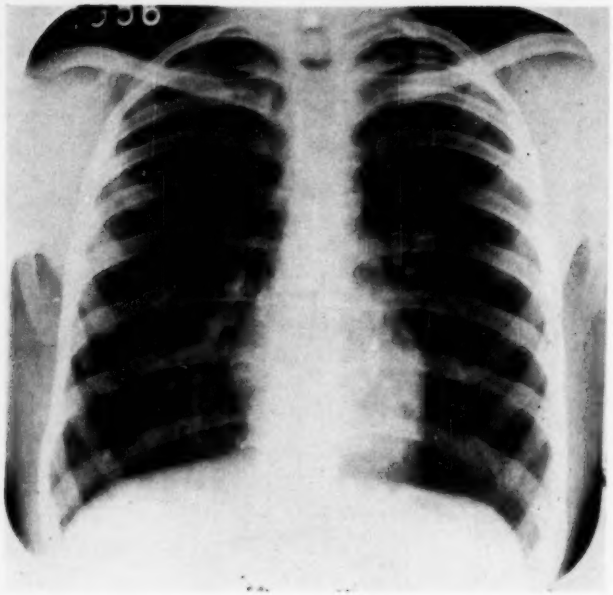

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Brit. J. Dis. Chest. (1960) **54**, 1.

EDITORIAL

THE opening of a new decade promises yet further stupendous changes in our preventive and therapeutic approach to intra-thoracic disease, including tuberculosis. The reappraisal, made necessary by modern chemotherapy, of many acute and chronic diseases within the thorax has previously been considered. To take, for example, tuberculosis, there is no doubt that modern anti-tuberculous drugs, evolved after meticulous research, have produced most remarkable results in relation to morbidity and mortality from tuberculosis in most parts of the world. Complacency in this field must, however, be avoided, for the problem is world-wide, and we must never forget that in many countries, with low standards of living, tuberculosis continues to be a major challenge.

Today there is no greater activity in any branch of medicine than in relation to diseases of the heart, lungs and mediastinum. The role of the pioneer Journal in this field of endeavour is more important perhaps than ever before in its history, and the whole field of intra-thoracic medicine from preventive, social, diagnostic and therapeutic angles has, of necessity, to be covered.

Advances in our subject are occurring so rapidly that the contribution of research to the clinical field becomes increasingly important. Professorial and other units, where new highly specialised techniques are being developed, should be of the greatest value equally to research workers and to practising clinicians.

Professor K. W. Donald (1959) in his inaugural lecture to the Edinburgh Faculty of Medicine rightly emphasises that " good clinical medicine cannot stand still. In bygone days important discoveries in biological science did not reach clinical medicine for decades or even centuries. Now they enter and challenge clinical procedure in a few months. We must, however, always remember that our final responsibility is to the patient, and that if new research is to be initiated then there must be an appropriate increase in staff and facilities so that each patient receives the same, if not more, personal attention."

There is no fundamental reason why first-class research should not be integrated with sound clinical medicine, and our dominant British reputation for medicine at the bedside might well be further enhanced by such a development. It is timely that in this issue much space should be devoted to tuberculosis, *e.g.* a critical review of " Immunity in Tuberculosis," " Some of the World Problems and Present Trends in Management," " An Analysis of Some Recent Work on Tuberculosis in Africa," etc.

Our next issue will be occupied by a symposium by distinguished experts on " Disordered Pulmonary Function," held under the auspices of the Faculty of Medicine of the University of Birmingham. The practical no less than the theoretical importance of methods of assessment of respiratory function cannot today be over-emphasised. The problem will be surveyed by Professor Melville

Arnott and there will be an authoritative consideration of ventilatory function, blood gas studies and the organisation of units for the assessment of respiratory function. Functional aspects of pulmonary disease which were inaugurated by Dr. Brian Taylor, including the disordered physiology of obstructive bronchial disease, alveolo-capillary block, management of respiratory infection, status asthmaticus, and assisted respiration in respiratory diseases will be discussed. Finally, a study of the lungs and heart disease inaugurated by Professor K. W. Donald, including a consideration of pulmonary hæmodynamics, pathology of pulmonary vessels, functional aspects of cor pulmonale syndrome, and the effects of surgery on pulmonary function should, all together, provide our readers with an intellectual feast and, let us hope, a stimulus for the coming decade.

P. E.

Brit. J. Dis. Chest. (1960) **54**, 3.

IMMUNITY IN TUBERCULOSIS

By J. M. Robson and F. M. Sullivan
Department of Pharmacology, Guy's Hospital Medical School, London

The first experimental demonstration of the development of immunity to tuberculosis was given by Koch at the close of the nineteenth century. He showed that the injection of tubercle bacilli into guinea pigs would produce an infection which rapidly spread to the regional lymph nodes and subsequently to other organs, ultimately leading to the death of the animal. If a tuberculous guinea pig was reinfected, however, there was the rapid development of a lesion at the site of reinoculation. This became necrotic and sloughed off, without any spread of the reinfecting bacilli to the lymph nodes. This heightened response at the reinoculated site, which is known as Koch's phenomenon, was soon shown to be the result of an allergic reaction by the guinea pig to the tubercle bacilli. For many years, in fact until the 1930's, this allergic response was considered to be the basis of the immunity, *i.e.* increased resistance, which is shown to tuberculosis. When more detailed investigations into the actual mechanisms involved in tuberculosis immunity were undertaken, however, it was soon realised that this was not the case and that, moreover, tuberculosis immunity was of a type quite unlike that which was responsible for the increased resistance to many other types of infection. This led to intensive investigations of the mechanisms of immunity to tuberculosis and also of the type of antibodies involved, and the next twenty years saw the accumulation of experimental results which, far from solving the problems, tended to make them even more complex.

Before attempting to approach the subject of specific resistance to tuberculosis, it is worth while to mention briefly some of the bodily changes giving rise to an increase in resistance, which may follow from non-specific stimuli.

After any infection, changes take place in the body which tend to cause a non-specific increase in resistance. For instance, the blood phagocytes may be stimulated into increased activity (Halpern, 1959) and they may also increase in number; this increased activity is helped by serum factors such as opsonins which assist in the rapid phagocytosis of foreign particles, and may be further stimulated by certain adjuvants (Freund, 1956), the mode of action of which we really do not know. Of particular importance in this respect is the general stimulation of the reticulo-endothelial system and the increase in resistance to non-specific infections produced by tuberculous vaccines or infection (Howard *et al.*, 1959; Dubos *et al.*, 1957; Dubos and Schaedler, 1957; Pullinger, 1936; Elberg *et al.*, 1957) and conversely, the increased resistance to tuberculosis which is produced by other non-specific infections (Nyka, 1957; Henderson *et al.*, 1956). Other workers (Youmans and Youmans, 1957; Swedberg, 1951), however, have failed to confirm some of these results that

(*Received for publication October* 1, 1959.)

non-specific vaccines will confer immunity against tuberculous infection and we (Acharya *et al.*, 1958) have shown that prior infection of mice with a variety of organisms failed to produce any detectable increase in resistance to subsequent tuberculous infection.

Immunity to Tuberculosis

That immunity does develop to tuberculosis was shown experimentally by Koch, but was known before and even cited as a law—"The Law of Marfan"—in 1886 (Marfan, 1886), in which attention was drawn to the fact that children who had recovered from tuberculous cervical adenitis rarely developed pulmonary tuberculosis in later life, and suggested that this was due to the development of immunity. The benefits obtained from immunisation have, however, frequently been contested and as recently as June 1959 (Anderson *et al.*, 1959) an article appeared in the *British Medical Journal* questioning the advantage of vaccination in tuberculosis. There is, however, an immense body of experimental evidence to show that vaccination can be of advantage in tuberculosis.

It seems desirable to describe what is known about the various factors involved in the development of immunity before considering the detailed mechanisms responsible for this phenomenon.

Experimental Investigations on Immunity

Numerous workers have studied the effect of previous vaccination with tubercle bacilli on the development of disease following reinfection. Generally one of three methods has been used to assess the degree of immunity present, namely (1) to measure the survival time of vaccinated animals when challenged with an inoculum of tubercle bacilli sufficient to kill all the animals in a control non-vaccinated group, usually within about one month, (2) to count and compare the number of bacilli in the organs of vaccinated and non-vaccinated animals at various times after challenge infection, and (3) to study the effects of vaccination on the development of macroscopic tuberculous lesions.

From the experimental data published we can make the following generalisations about the immunity produced following vaccination or infection with tubercle bacilli. These will be considered under the general headings of: species, vaccines, dose of vaccine, route of vaccination, rate of development of immunity, duration of immunity and degree of protection.

Species

The species so far studied which do show the development of immunity include mice, voles, rats, hamsters, guinea pigs, rabbits, fowls, goats, dogs, sheep, swine, cattle, monkeys and man. All of these, with the possible exception of mice and rats, show to varying degrees the concomitant development of allergic hypersensitivity along with the development of immunity. Mice do not normally show any hypersensitivity to the tubercle bacillus, although Gray

and Jennings (1955), using a special technique, have demonstrated an allergic response to tuberculin in infected C57 black mice, and Hart *et al.* (1952) have shown that tuberculous mice are more sensitive to the toxic effects of tuberculin than are normal mice. Mice can, nevertheless, show a marked development of immunity to tuberculosis after vaccination without any evidence of the development of allergy, so that this animal does provide a useful means of studying the mechanism of immunity without the superimposed complication of hypersensitivity.

Vaccine

The human, bovine and murine types of *Mycobacterium tuberculosis* will all confer increased resistance to reinfection with each other. It is generally agreed that virulent strains confer greater protection than non-virulent strains, though there is some disagreement about this and also whether the attenuated bovine strain BCG will confer more or less immunity than the avirulent human strain H37Ra. This latter strain does confer marked immunity and yet is usually a non-multiplying organism *in vivo*, so that obviously the ability to multiply is not a prerequisite for the production of immunity. Killed organisms will also confer immunity against reinfection, but variations in the method of killing produce differences in antigenicity. Several workers have found phenol killed organisms to be superior to heat killed organisms, and nitrous acid killed BCG has been reported (Mukozaka, 1957) to be as effective as live BCG, but many other factors, such as the *p*H of the medium used for suspension during heat killing, will affect the antigenic properties of the bacilli (Swedberg, 1951). In any case, the number of killed organisms required to produce any degree of immunity is always greater than the number of live organisms required. The immunogenic property of killed mycobacteria is fully reviewed by Weiss (1958, 1959). Other live mycobacteria have also been demonstrated (Swedberg, 1951) to confer increased resistance against infection with mammalian tubercle bacilli. Two of these are *Mycobacterium tuberculosis* var. *ranæ* (frog bacillus) and *Mycobacteria tuberculosis* var. *avium*. *Mycobacterium phlei* (timothy bacillus) did not increase the resistance of the guinea pigs tested. It is interesting to note in this connection that Suter (1955) reports that *Mycobacterium X* (an attenuated avian strain) confers increased resistance in monocytes of guinea pigs and yet does not produce hypersensitivity in these animals. Fenner (1957), using a technique of footpad infection in mice, found that *M. Balnei*, *M. ulcerans* and BCG all immunised against infection with *M. Balnei*, *M. ulcerans* and *M. avium*. *M. ranæ* and *M. phlei* failed to protect against *M. Balnei*, and while BCG and *M. avium* protected against the virulent bovine strain—Branch, *M. Balnei* and *M. ulcerans* did not. There are also reports (Elberg *et al.*, 1957; Bekierkunst and Sulitzeanu, 1958) of cross-resistance between Brucella and Mycobacteria.

Dose of Vaccine

It seems reasonable to assume *a priori* that, within reasonable limits, the bigger the dose of vaccine used the better the immunity produced, but in fact

there is some disagreement between various workers on the effect that variation of the vaccinating dose has on the resultant immunity. In guinea pigs vaccinated with doses of BCG ranging from $\frac{1}{100}$ to ten times the dose used for human vaccination, a progressive increase in immunity has been obtained (U.S.P.H.S., 1957). Similarly in mice a progressive inhibition of the development of corneal tuberculous lesions has been produced by varying over a thousand-fold range the vaccinating dose of BCG given intravenously (Goulding, 1957). Bloch and Segal (1955) obtained similar results using dilutions of BCG and H37Ra varying over a thousandfold range, using survival time as criterion. On the other hand, in experiments in which mice were vaccinated intracorneally with varying doses of a virulent bovine strain and challenged in the other eye with the same strain, no correlation between the vaccinating dose and the immunity produced has been observed (Acharya *et al.*, 1958). This was in agreement with other experiments (Swedberg, 1951) in which mice were vaccinated subcutaneously with doses ranging from 0·05-3·2 mg. of a virulent human organism and again no difference in protective effect was seen. Dubos *et al.* (1953) found little effect with a variation in vaccinating dose of 100-fold. It is unlikely that the discrepancy in these results is due only to a strain difference in the animals used, since Goulding (1957) and Acharya *et al.* (1958) used mice from the same stock. The first worker quoted above, however, used BCG, whereas the latter used a virulent strain for vaccination, and this may account for some of the differences in their results. With killed vaccines larger doses are always required to produce an increased resistance, and there must obviously be some relationship here at least between dose and effect.

In the Medical Research Council clinical trials of BCG and vole bacillus vaccines (1959) in adolescents, variation in the viable counts of BCG vaccine produced a graded response with regard to the development of hypersensitivity, but no difference was seen in the actual protection produced.

Route of Vaccination

Immunity has been successfully produced in animals following intravenous, intraperitoneal, subcutaneous, intradermal and intracorneal inoculation and after oral and paranasal administration. It is not feasible to compare the results of different workers with reference to the degree of immunity obtained by the various routes, because of the large number of other variables, but Swedberg (1951) found that there was no significant difference between intravenous and intraperitoneal vaccination, both these routes being better than the subcutaneous route. Acharya *et al.* (1958) found no difference between the intracorneal and intradermal routes. Bloch and Segal (1955) found that in mice the intraperitoneal route gave more immunity than the intravenous route, but Dubos *et al.* (1953) showed that the intravenous route was better than the intraperitoneal and both of these were much better than intramuscular or subcutaneous vaccination. Ch'Iao Shu-Min (1957) found in guinea pigs that the intranasal, the oral and the intradermal routes were all equally

effective, whereas Drabkunova and Sukhodol'Skaia (1957), also using BCG in guinea pigs, found the oral route to be ineffective.

In man the oral route of vaccination was the one classically introduced by Calmette in 1921 (Calmette, 1928), and this route is still used in Russia and other East European countries (Lapina, 1955) and in certain middle and South American countries. In a review of this method of vaccination, De Assis (1957) concludes that it is less effective in infants than parenteral vaccination, and this supports the observations of Kereszturi and Park (1936) who also found better protection from BCG when given parenterally to children as compared with oral administration. As far as the various methods of parenteral vaccination are concerned, there would seem, from the results published so far, to be little advantage as far as ultimate protection is concerned to be derived from any particular route, though there is no evidence that the duration of the immunity will be the same following different routes of vaccination, and this is one of the problems which we intend to investigate in the near future.

Rate of Development of Immunity and its Duration

In mice, various workers (Bloch and Segal, 1955; Goulding, 1957; Acharya *et al.*, 1958; Swedberg, 1951; Fenner, 1957) have shown that an increase in resistance following vaccination is demonstrable within the first week. In one detailed study (Acharya *et al.*, 1958) some immunity was observed when mice were challenged two days after vaccination, but not on the first day after vaccination. Dubos and Pierce (1956b) showed slight protection by two days after immunisation with a very large dose of BCG, and Bloch and Segal (1955) reported some immunity to a challenge given three days after BCG vaccination. It must be realised, of course, that the effect of the challenge infection is not observed for some time after it is given, so that the fact that one observes an increase in resistance to an infection given two or three days after vaccination need not mean that any appreciable immunity has developed by the second or third day. In mice the degree of immunity gradually increases after vaccination and reaches a peak somewhere about one month after vaccination. Bloch and Segal (1955) reported a peak at three to six weeks after vaccination, and Acharya *et al.* (1958) showed (by using a sufficiently large challenge dose) that the immunity was still increasing between the fourth and eighth week after vaccination. The duration of immunity is variously reported by different workers so that for instance Goulding (1957), using intracorneal challenge to mice vaccinated intravenously with BCG, showed some decrease in the immune level eight weeks after vaccination and a very marked reduction in immunity twenty-eight weeks after vaccination. Bloch and Segal (1955) report complete loss of immunity by nine months, as judged by survival time after intraperitoneal vaccination with BCG and intravenous challenge. On the other hand, Dubos and Pierce (1956b) reported persistent immunity in mice eight months after intravenous vaccination and Acharya *et al.* (1958) demonstrated the presence of immunity thirteen months after intradermal vaccination. These various results should not be compared too closely because of the different

modes of immunisation and challenge used by the different workers; moreover, as will be shown in the next section, the degree of immunity which can be detected depends very much on the type of challenge used.

In guinea pigs there are fewer results available, but Swedberg (1951) failed to show any immunity fourteen days after vaccination subcutaneously with BCG, though definite immunity could be shown thirty-four days after vaccination and this persisted for at least seventy-seven days. Wells and Wylie (1952) showed that hypersensitivity was present about nine days and lasted about ten months after BCG vaccination, though immunity lasted much longer when the vaccine used was the vole bacillus. Lack (1956) showed that hypersensitivity developed within one week following injection of the virulent strain H37Rv, but later after the avirulent strain H37Ra.

In man, allergic hypersensitivity develops about four weeks after vaccination with BCG which probably coincides with, although it may even follow, the development of increased resistance. The duration of immunity is not known accurately, but Lorber and Menneer (1959) report that of 248 children examined, 243 (98 per cent.) were still Mantoux positive at least five years and in some cases nine years following BCG vaccination, though these children were all contact cases. Bacigalupo de Lucero *et al.* (1955) revaccinated children three to four years after BCG vaccination and found that a higher proportion gave an early positive reaction (sixth day) to BCG than the proportion giving a positive Mantoux reaction, and in the Medical Research Council trial of BCG (1959) there was persistence of hypersensitivity up to at least six and a half years in some cases. The relation of the Mantoux reaction to immunity will be discussed later. Whether the duration of immunity depends on the persistence of bacilli in the body is not known, but Bloch (1955) gives some evidence that this may be the case, and thus suggests that it may not be desirable to eradicate completely an infection in man. This is supported by the observation of Dubos and Pierce (1956b) in mice that BCG-A persists in the tissues for many months and produces a long lasting immunity compared with BCG-B which is quickly cleared from the tissues and produces only a short lasting immunity.

Degree of Protection

In contrast to many other types of immunity, that developed against tuberculosis is considerably restricted in degree. That this is so is evidenced by the fact that there are still many people who question the advantage of BCG vaccination. Also, patients who have had clinical tuberculosis are liable to reinfection. In experimental tuberculosis, animals which have been vaccinated may show increased resistance to reinfection with a small challenge dose of virulent bacilli, yet may fail to show any immunity, or a decreased immunity, when challenged with a larger dose of organisms. This was shown by Okell and Parish (1928) to occur in guinea pigs, and numerous other workers (Swedberg, 1951; Youmans and Youmans, 1957; Acharya *et al.*, 1958) have since confirmed this for guinea pigs and mice. While this is well recognised as a hazard in the interpretation of immunity experiments by most research

workers engaged in this field, it is not always appreciated by others. Thus, for example, there is considerable controversy as to whether killed organisms are capable of producing immunity, and evidence has been published showing both the development and the absence of immunity after vaccination with killed mycobacteria. Now the immunity produced by dead bacteria is very probably of a low order compared with that produced by similar numbers of live bacteria, and if a heavy challenge dose of virulent organisms is given to try to demonstrate an increased survival time, then the small amount of immunity present may be completely swamped by the challenge. On the other hand, if some other criterion of immunity is used which utilises a smaller number of virulent organisms in the challenge infection than are required to kill the animal, then definite immunity may be observed. This limited development of immunity to tuberculosis accounts for the observations made in man that live BCG vaccine will confer considerable protection against infection with virulent organisms, but that people living in heavily infected surroundings are still liable to develop clinical tuberculosis on reinfection. The problem has also been discussed by Youmans and Youmans (1957).

Factors involved in the Mechanism of Immunity

The Relation of Allergy to Immunity

The relation between allergy and immunity has been discussed at great length since Koch's demonstration of the development of hypersensitivity to the tubercle bacillus. The experimental evidence has been thoroughly reviewed by Rich (1951) and summarised as follows: " . . . The more recent studies on tuberculosis and other infections . . . have now provided a large body of evidence that acquired resistance is not dependent upon hypersensitivity." Evidence is given that there is no correlation between hypersensitivity and degree of acquired resistance and that the hypersensitive inflammation is incapable of preventing the early spread of the bacteria in the absence of acquired resistance. Furthermore, immunity can develop without hypersensitivity and remain after hypersensitivity has gone, either naturally or in desensitisation experiments (Yanagisawa *et al.*, 1956). It is fairly well established now that immunity and allergy are two distinct phenomena. Raffel (1950) in a study of chemical factors involved in the induction of infectious allergy quotes experiments on three groups of guinea pigs. One group was immunised with BCG, the second with appropriate doses of tuberculoprotein and wax, and the third left untreated. Some time later these groups were tested with Old Tuberculin and the first two groups showed a marked and equal positive response and the third (control group) was negative. They were all then challenged with a virulent bovine strain of tubercle bacillus both intra- and subcutaneously. The result is shown in Table 1. An equal and definite Koch's phenomenon was seen in both of the first and second groups showing the presence of hypersensitivity, but when the animals were killed eight weeks later, examination of the extent of disease in various organs showed the presence of marked immunity in the BCG vaccinated group, but

TABLE I.—COMPARISON OF ALLERGIC AND IMMUNE RESPONSES IN GUINEA PIGS SENSITISED WITH BCG AND WITH TUBERCULOPROTEIN-WAX

Group No.	*Treatment of animals*	*Average reactions to O.T. (mm.)*	*Average Koch reactions (mm.)*	*Tuberculous involvement of organs*		
				Lungs	*Liver*	*Spleen*
1	BCG	13·0	6·0	±	0	0
2	Protein-wax	12·8	4·1	2+	2+	3+
3	None	0	0	3+	2+	4+

According to Raffel (1950).

no evidence of any immunity in the group treated with protein and wax, the extent of the disease in this latter group being the same as in the control group. He concludes that the bacillary constituents which engender allergy are not the same as those which produce increased resistance to infection, and that tuberculous allergy and resistance are not synonymous. Experiments similar to that of Raffel have been previously reported by Choucroun (1949), who has isolated a lipo-polysaccharide (PMKO) from tubercle bacilli which will produce a marked increase in resistance in guinea pigs without the development of hypersensitivity, though we have been unable in this laboratory to demonstrate any immunising activity with PMKO, using the corneal technique in mice (unpublished observations).

Youmans *et al.* (1955, 1957) have isolated immunogenic particles by centrifugation at 144,700G (40,000 r.p.m.) of ground-up avirulent tubercle bacilli, and preliminary results have shown that these particles can produce immunity in guinea pigs without sensitising them to tuberculin (Youmans, 1957).

Suter (1955) has also shown that guinea pigs immunised with the avian strain *Mycobacterium X* will develop immunity without hypersensitivity, and Fenner (1957) has shown a similar relationship in mice, *i.e.* that BCG vaccination will produce immunity to reinfection with *M. Balnei* without the development of hypersensitivity (as demonstrated by the footpad test), whereas vaccination with *M. Balnei* gave both immunity and hypersensitivity to reinfection with the same organism. Wells and Wylie (1952) demonstrated that in guinea pigs there was persistence of immunity for a considerable period after hypersensitivity was lost. Further evidence of a different type in support of this independence of allergy and immunity was given by experiments on mice (Robson *et al.*, 1957), where marked immunity sufficient to inhibit completely the multiplication of the organisms of the challenge infection was produced without any evidence of hypersensitivity and in fact with a cellular reaction which was considerably smaller than that produced by a primary infection.

In humans too it would seem that the development of hypersensitivity is not a necessary prerequisite for the production of immunity. Thus in the M.R.C. trials of BCG and vole bacillus vaccines (1959) it was found that the

larger the number of viable BCG organisms injected the higher the percentage of children showing a positive Mantoux reaction, yet there was no concomitant increase in the actual protection produced. This was even more strikingly demonstrated when the vole bacillus vaccine was used. When a low dose of vaccine was given, there was only a 31 per cent. conversion to 3 T.U. and a 56 per cent. conversion to 100 T.U., yet the protection given was as good as, if not better than, that produced by a dose of BCG which gave a 97 per cent. conversion to 3 T.U. This does not mean that the Mantoux test is valueless as an indicator of immunity, since the majority of people who have been infected either clinically or by vaccination with the tubercle bacillus have been exposed to all of the antigens of that organism, and so if they do show the presence of hypersensitivity to tuberculin, then clinical experience has shown that they will also probably have an increased resistance to reinfection. It has also been demonstrated in guinea pigs (Jespersen, 1956) that while hypersensitivity is always accompanied by immunity following BCG vaccination, there is no correlation between the size of the tuberculin reaction and the degree of protection. On the other hand, it should not be assumed that if a person does not show the development of hypersensitivity after vaccination he has not developed an increased resistance to infection. Not only may an immunised person not develop hypersensitivity after vaccination (as in some cases with the vole bacillus vaccine), but it has also been shown that hypersensitivity as judged by the Mantoux test may disappear after some years, and yet the person still be sensitive to live tubercle bacilli (Bacigalupo de Lucero *et al.*, 1955). Such observations have in fact led to the suggested use of a " BCG test" instead of a tuberculin test (Genz, 1957) utilising BCG instead of tuberculin, since such a test shows up the presence of allergy at a lower level than does the Mantoux test. Furthermore, the experimental and clinical observation that immunity can be produced without allergy has led to a widespread body of opinion that the development of a non-sensitising vaccine against tuberculosis would be a most useful one, since the diagnostic value of the Mantoux test would not then be lost due to vaccination.

The Role of Humoral Factors in Immunity

The sera of tuberculous or immunised animals and man do contain antibodies which will react with tubercle bacilli and certain fractions of tubercle bacilli. The serum of immunised animals will produce agglutination of tubercle bacilli *in vitro*, promote phagocytosis by polymorphs or monocytes *in vitro*, fix complement in the presence of tubercle bacilli, and form precipitates with protein and carbohydrate fractions of tubercle bacilli. However, even in the presence of complement it has no bactericidal or lytic effect on tubercle bacilli (Dubos, 1952). The relation between these antibodies and increased resistance has been closely studied by Raffel (1955) and his experiments included tests of complement fixation, agglutination, agar diffusion precipitation, hæmagglutination, hæmolysis and Coombs test for incomplete antibodies. He performed these tests on sera of guinea pigs which had been vaccinated with bacilli both alive and killed by various means, and also with various fractions of bacilli,

some of which produced immunity and hypersensitivity and others which produced hypersensitivity without immunity. Where positive serological reactions occurred, he never found either qualitatively or quantitatively any difference between the sera of these animals which developed immunity and those which were vaccinated with substances which did not produce immunity. In other words, he never found any serological reaction which gave any indication of the presence or absence of immunity as opposed to hypersensitivity. It may well be, of course, as Raffel himself points out, that the present serological tests are insufficient for the detection of the specific immune antibody to tubercle if it in fact exists. This problem is also discussed by Seibert and Seibert (1957) and Seibert (1958).

One of the most important pieces of evidence which casts doubt on the presence of a serum factor in immunity is the failure to transfer passive immunity to tuberculosis by transfusions of serum. Once again, however, there is conflicting evidence with regard to the result of the transfer of the serum or blood from tuberculous and non-tuberculous animals to other infected animals. The earlier work in this field has been reviewed by Rich (1951).

Raffel (1955) reports the results of two experiments (performed with Efford) in guinea pigs, in the first case with a mild tuberculous infection and in the second with a more severe infection. They injected groups of these animals with serum or whole blood from normal and BCG vaccinated guinea pigs (2 ml. subcutaneously daily for two months), but failed to find any protective effect at all from the injections. On the other hand, Zitrin and Wasz-Hockert (1957) published preliminary experiments on the transfer of a protective humoral antibody in the serum of tuberculous patients to mice, and showed a protective effect in prolonging the survival time of mice infected intravenously with the Vallee strain of tubercle bacillus. The serum also inhibited the growth of H37Rv *in vitro*. The data given in that paper are insufficient for a statistical evaluation of the significance of the protective effect, but the investigations are being continued and further publications by these authors should prove interesting.

Another line of approach to the detection of humoral factors is that which follows the multiplication of bacilli situated extra-cellularly in the body either in semi-permeable capsules or otherwise. Lurie in 1936 (Lurie, 1936) put forward evidence that in immune rabbits a humoral factor was present which inhibited the multiplication of organisms kept extracellular by being embedded in agar, whereas no such inhibition was seen in normal rabbits. He added, however, that the most significant factor in immune rabbits was an increased power of the monocytes to inhibit multiplication. He later repeated these experiments (Lurie, 1939a) with guinea pigs and got the same result, suggesting again the presence of a humoral factor. In the experiments described in this latter paper he also demonstrated the presence of an inhibiting humoral factor, by implanting the bacilli in bags made of silk impregnated with collodion into rabbits. Raffel (1955) performed similar experiments in which he enclosed virulent tubercle bacilli in plastic capsules and covered the end with

a Gradocol filter (porosity 60-70 mμ). These were implanted intraperitoneally in normal and immune guinea pigs and the contents of the capsules counted at intervals up to three months. Raffel failed to demonstrate any difference in the multiplication of the bacilli in the capsules implanted in either the immune or normal guinea pigs.

More recent studies in Japan by Shusuke Tsuji and his co-workers have been made (Tsuji *et al.*, 1957; Tsuji *et al.*, 1958) using a semi-permeable chamber implanted into the peritoneal cavities of a wide variety of animals. Their results are substantially in agreement with those of Lurie—that the serum of immunised animals has a marked inhibitory effect on the multiplication of bacilli kept extra-cellular in the chamber. Tsuji *et al.*, however, carried these experiments a stage further. They used two types of chamber, one of which would allow the passage into it of proteins and the other which would pass only the low molecular fraction of serum. By the use of these differential chambers and by complementary *in vitro* experiments they were able to give evidence that in rabbits the inhibitory power of immune serum was due, not to the development of an inhibitory substance, but to the reduction of a growth promoting substance in the higher molecular fraction of body fluid. Furthermore, they found no difference in the growth inhibitory function of the lower molecular fraction of body fluid between immunised and control rabbits. It may be that the reduction in serum albumin which is seen in many tuberculous animals in part accounts for the inhibitory effect of immune serum.

Finally, in the investigation of a humoral factor in immunity there is some evidence obtained by testing for inhibition of growth of mycobacteria *in vitro*. Some early workers, *e.g.* Pagel (1935) and Kallós and Nathan (1932), showed the presence of inhibitory substances in serum. Other workers, *e.g.* Lurie (1939b) and Suter (1953), did not find in their studies on monocytes *in vitro* that the source of the serum used was very important. Similarly Hanks and Evans (1940) failed to show any effect of immune serum *in vitro*. Myrvik and Weiser (1951) demonstrated the development of a non-antibody lysozyme-like substance which was bacteriostatic for tubercle bacilli in the serum of rabbits following immunisation with mixtures of killed tubercle bacilli and Freund's adjuvant. The substance, however, was not specific for tubercle bacilli, and extensive studies by Youmans and Youmans in conjunction with Myrvik and Weiser (Weiser *et al.*, 1958) failed to show any protective effect of crystalline egg white lysozyme against experimental tuberculous infection in mice. Recently Kotani *et al.* (1956a and b) showed an inhibitory action of immune serum against tubercle bacilli which was short-lived (only for 24 hours), and this was believed by them to be due to the rapid inactivation of complement at 37° C. It may be for this reason that the more recent experiments of Tsuji *et al.* (1958), using a system in which the serum was changed every two or three days, were successful in showing an inhibitory effect of immune serum *in vitro*, though it must be repeated that this inhibition may be due to a reduction in growth promoting power of the serum and not in increased growth inhibiting power. Hubáček and Málek (1959) in Czechoslovakia arrived at a conclusion very similar to that of Tsuji, using a different technique of micro-

culture in which serum was again changed every two days. The multiplication of single organisms into micro-colonies was used as an index of multiplication. They also demonstrated a marked inhibitory power of immune rabbit serum against tubercle bacilli and this inhibitory effect was not removed by heating at 56° C. for 30 minutes (*i.e.* presumably by the inactivation of complement). They found that there was good growth of BCG in normal serum, but that this could be prevented by prior adsorption of the serum with concentrated suspensions of live or dead mycobacteria. This was attributed by them to the removal by the organisms of a growth promoting factor, and electrophoresis showed disappearance of the α-globulin in this adsorbed serum. Thus, while there is still no conclusive evidence for the presence of a humoral factor in tuberculosis immunity, the present evidence is suggestive that this may be the case.

The Role of Cellular Factors in Immunity

The earlier failures to demonstrate humoral antibodies against mycobacteria led to the investigation of the macrophages to see if the immunity was a result of an increased inhibitory power of these phagocytes. After a primary infection with virulent bacilli the organisms soon become intracellular within macrophages. The organisms multiply quite readily and rapidly within these cells, eventually overgrowing and bursting out of the cells, to be rephagocytosed by other macrophages. When an immunised animal is infected, however, the bacilli are rapidly phagocytosed by macrophages, but, in contrast to the non-immune animals, the bacilli do not multiply but remain viable and quiescent inside the macrophages for considerable periods (Robson *et al.*, 1957). To test whether macrophages in immune animals possess an increased capacity to inhibit mycobacterial multiplication, Lurie (1942) allowed monocytes from normal and immune rabbits to phagocytose virulent tubercle bacilli *in vitro* both in the presence of immune and non-immune serum. He then injected these cell suspensions into the anterior chambers of normal rabbits—one eye with immune cells plus bacilli and the other eye with normal cells plus bacilli. The multiplication of the organisms was then determined both by plate counts and by microscopic examination of sections of the eyes. He found that there were always far fewer bacteria in the anterior chambers of the eyes containing immune cells than in those containing non-immune cells, irrespective of the type of serum used initially for the phagocytosis. Raffel (1955) performed similar experiments in which normal and immune guinea pig monocytes and bacilli were enclosed in capsules and implanted intraperitoneally in normal and immune guinea pigs. He was, however, unable to show any inhibitory effect of immune macrophages as compared with normal macrophages.

Numerous experiments have also been performed *in vitro* to try to demonstrate any difference between growth of mycobacteria in normal and immune macrophages. The three main protagonists in this field are Suter (1953, 1954), Mackaness (1954) and Raffel (1955). Suter and Raffel both demonstrated an increased inhibitory power of macrophages from immune animals (guinea

pigs), whereas Mackaness using rabbit monocytes was unable to demonstrate this inhibition. When these three workers studied the multiplication of attenuated and avirulent strains in normal monocytes, however, they all managed to disagree with each other and each has criticised the experiments of the other. Brieger (1951) has also published some experimental results with tissue explants *in vitro* which support the results of Suter. The reason, however, for all of the controversial results from the *in vitro* experiments must surely lie to some extent at least in the lack of sufficiently precise technical methods for the study of cells in culture media. Fong and his co-workers (Fong *et al.*, 1956, 1957; Elberg *et al.*, 1957; Fong *et al.*, 1959) have shown that one must consider not only the effect of the cells on the bacilli but also the effect of the bacilli on the cells. They have shown that virulent organisms of the strain H37Rv have a marked necrotising effect on normal rabbit monocytes in normal serum or in serum of animals immunised with BCG, but not on immune monocytes in immune serum. The serum factor necessary for the protection of immune cells, however, is non-specific, since serum from animals immunised with a number of organisms other than mycobacteria, or even with ovalbumin, is effective. In their experiments they were unable to show any difference between the rate of multiplication of H37Rv in normal rabbit monocytes in normal serum and in immune monocytes in immune serum—in both cases there was a 16 to 18-fold increase in numbers of intra-cellular bacilli after six days' culture (Fong *et al.*, 1959). Thus, although it is evident that *Mycobacterium tuberculosis* shows decreased multiplication in the macrophages of immune animals *in vivo*, as compared with non-immune animals, it remains to be established whether this is purely a function of the cells or whether extracellular factors are also involved.

Other Factors involved in the Development of Immunity

There are other factors involved in the development and action of anti-tuberculous immunity of a type different from those considered previously for other classical immune systems. These include the differences in oxygen availability to the tubercle bacilli in normal and immune hosts, the non-specific stimulation of the reticulo-endothelial system by tuberculous vaccines, and the influence of hormones. The effects of adreno-cortical factors which have been investigated and have been reviewed by Lurie (1955) will not be considered here.

Effect of Oxygen Tension

The tubercle bacillus is an obligate aerobe and a good oxygen supply is necessary for a luxuriant growth of the organisms (Webb *et al.*, 1924; Novy and Soule, 1925). However, the organisms can continue to multiply and metabolise even under extremely low oxygen tensions provided that the total volume of oxygen present is sufficient. Under oxygen tensions sufficiently low to allow the growth of obligate anaerobes it has been reported that tubercle bacilli are able to vegetate, and after being kept in such a condition for twenty-

eight days the organisms are able to multiply and produce a good culture on being returned to an atmospheric oxygen tension (Novy and Soule, 1925). Loebel *et al.* (1933), using the same human strain (H37) as Novy and Soule, were, however, unable to support the claims of these previous authors as to the effect of anaerobiosis on the subsequent regeneration of the organisms when transferred to higher oxygen tensions. They found, in fact, that seven days of anaerobiosis usually prevented any subsequent regeneration of the bacilli. Furthermore, they showed that the tubercle bacillus lacks an anaerobic glycolytic mechanism, whereas mononuclear phagocytes do not. They calculate that in the centre of a tubercle 0·075 mm. to 0·35 mm. radius, complete oxygen lack may occur, and that the effect of this on the tubercle bacilli, by inhibiting their metabolism, may be an important factor in limiting the course of the disease. Studies by Kempner (1939) on the relation between oxygen tension and oxygen consumption showed a progressive depression of oxygen consumption with reduced pressure, and in his discussion he emphasises that both oxygen tension and the absolute amount of oxygen available are important factors in the growth of the tubercle bacillus. These *in vitro* experiments provided evidence in support of similar suggestions based on *in vivo* and *in vitro* results of Corper and Lurie (1926) and Corper *et al.* (1927) and further support for this hypothesis, *i.e.* the significance of oxygen lack on limiting the development of tuberculosis, has been given by Dubos and Pierce (1956a) and Sever and Youmans (1957). Direct experimental evidence of the effect on the tuberculous infection of subjecting the animal to low oxygen tension was given by the work of Rich and Follis (1942). Tuberculous guinea pigs living in an atmosphere of 10 per cent. oxygen showed practically no evidence of infection when killed after one month as compared with control animals kept under normal atmospheric conditions. This result was confirmed by Ong *et al.* (1948) in guinea pigs, while Sever and Youmans (1957) showed a marked increase in survival time of tuberculous mice kept in an atmosphere of 10 per cent. oxygen.

Further evidence in support of the importance of adequate oxygenation in the development of tuberculosis was given by Adams and Vorwald (1933), who showed that, following experimental infection, much less tuberculosis develops in the lobe of a lung in which oxygenation is reduced by blocking of a bronchus. Conversely, systemic pulmonary arterial anastomosis in monkeys results in worsening of tuberculous infection in the lung or segment of lung which is " arterialised " (Olsen *et al.*, 1952), and the investigators suggest that this is not due to the increased blood flow, blood pressure or unequal recirculation of the bacilli, but to the high oxygen tension in the " arterialised " segment.

It has been suggested that the commonly observed apical localisation of pulmonary tuberculosis in man is due to the poor blood supply to this region, since the pulmonary arterial pressure in the lung apex in man may be zero. This would prevent good gas exchange in the apex, with the result that apical alveolar air would have a high oxygen content similar to that in the trachea (Dock, 1946). This is not the only factor, however, since there will also be poor lymph formation and thus slow penetration of any humoral antibodies

and slow removal of toxic products. This localisation of disease to the highest part of the lung is not restricted to man, moreover, since in rabbits progressive cavitary lesions are also most commonly found in the highest (dorsal-inferior) region of the lung, and if the rabbits are suspended in the vertical position the lesions are then localised in the apical (cephalic) part of the lung (Medlar and Sasano, 1936). Similarly in the flying fox (*pteropus*), which normally lives head downwards, Francis (1958) quotes the observation of Rothlin and Undritz that tuberculosis is most commonly localised in the caudal portions of the diaphragmatic lobes.

There is, however, a factor, other than blood flow, which would limit the amount of oxygen available for the tubercle bacilli in an immunised host. The reinfecting organisms are quickly taken up by mononuclear phagocytes, and it has been suggested that metabolic activity of the monocytes may deprive the bacilli, contained within their cytoplasm, of oxygen to a degree sufficient to inhibit their multiplication. Raffel (1955) has shown in some preliminary experiments that the macrophages of immunised guinea pigs have an increased oxygen consumption as compared with those of control guinea pigs, and Howard *et al.* (1959) have shown that BCG vaccination increases not only the phagocytic activity of reticulo-endothelial cells, but also enhances their metabolic activity. It is difficult to draw general conclusions from all of these experiments about the exact role of oxygen tension in the mechanism of tuberculous immunity. We can, however, suggest that, other factors being equal, any measure which would reduce the amount of oxygen available for the tubercle bacillus in the host would retard the multiplication of the organisms and so produce a beneficial effect on the course of the disease. It is probably by this mechanism that collapse therapy has proved in the past to be so helpful in the treatment of tuberculosis.

Organic Acid Concentration

It has been suggested (Dubos, 1950, 1953) that the high local concentration of organic acids (particularly lactic acid) at an inflammatory site may be responsible for the inhibition of tubercle bacilli within such lesions. If this were the case, however, then allergic reactions to the bacillus involving inflammation and presumably the production of lactic acid would be expected to be important in the control of infection, but the work of Rich and Raffel previously referred to shows that allergy alone may not be sufficient to inhibit the development of tuberculous infections. Nevertheless, lactic acid does accumulate at inflammatory sites and Dubos has shown that this substance is toxic for the tubercle bacillus, particularly under anaerobic conditions. Since this is mainly a bacteriostatic action, however, it will not be sufficient to sterilise a tuberculous focus in the absence of other host defences, but will all the same represent a valuable adjunct to the immunological factors responsible for the final removal of the bacilli. From the work of Loebel *et al.* (1933) and of Dubos (1950) it would seem that this effect of organic acids is not so much due to the alteration in *p*H produced by the acids, as to a direct toxic effect of the compounds themselves.

Effect of Sex on Immunity

There have been many reports on the influence of sex and sex hormones upon the natural resistance of various species to infection with tuberculosis (Lurie *et al.*, 1949a, b, c; Aycock and Foley, 1945; Long and Vogt, 1941). Most of these reports are, however, conflicting, and where marked effects have been produced by sex hormones, very large doses have been used. Investigations of their influence on the development of immunity, however, are fewer in number. Perla and Marmorston (1941) quote the work of Gray and Brack (1939) that they were unable to detect any effect upon acquired resistance to tuberculosis in guinea pigs kept in a state of hyperœstrus by the injection of œstrogen. Swedberg (1951) also found no consistent difference between males and females in the immunity produced in guinea pigs by vaccination with BCG. However, treatment with large doses of œstrogen both increased the severity of tuberculous infection and depressed the development of immunity to reinfection. Hoyt *et al.* (1957), however, showed a very striking difference in the protective effect of BCG in male and female mice. While immunisation of males produced a very marked prolongation of survival time after challenge, the females showed practically no difference between vaccinated and non-vaccinated groups, and the females were also slightly more susceptible to a primary infection than the males. In man there is no published evidence of any difference in the immunity produced by vaccination between males and females. This lack of published evidence amongst such a wealth of other information suggests perhaps that no differences have been found. In the M.R.C. trial of BCG and vole bacillus vaccines (1959) no difference was observed in protection rates between males and females (M.R.C.—Tuberculosis Research Unit—personal communication).

General Conclusion

It is obvious that both specific and non-specific factors can modify the resistance to tuberculosis, as they can to other infections. Immunity as a rule gives only partial protection, though under favourable circumstances complete inhibition of multiplication of a small inoculum can be achieved. The mechanism of immunity in tuberculosis has been extensively studied and appears to be different from that operating in many other infections. Evidence for the participation of both cellular and humoral mechanisms has been obtained, but there is no doubt that further research on the subject is required.

Summary

Many of the factors involved in the production and mechanism of immunity to tuberculosis are reviewed. Results of experimental work in animals are given in some detail and where possible are correlated with observations in man. The results differ somewhat in detail between various species, but in general a wide range of mycobacteria will protect against tuberculous infection, though the degree of protection varies, and at best is never as good as that seen

in certain other infections, *e.g.* diphtheria or smallpox. Immunity develops within a week or so after vaccination and gradually increases in intensity during the first two months. The duration of immunity seems to vary depending on the vaccine, route of vaccination used, and possibly species, though in man at least it seems to last for more than six years. The relationship between allergy and immunity is discussed and evidence is given that these are independent phenomena and that either can exist in the absence of the other. Clinically the importance of this is that failure to convert to Old Tuberculin after BCG vaccination need not mean that good protection has not been developed, and in fact it is demonstrated that humans can show good protection in the absence of hypersensitivity. The cellular and humoral factors involved in immunity to tuberculosis are discussed, as are also the effects of oxygen tension, local organic acid concentration, and the effect of sex.

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TUBERCULOSIS TODAY

SOME OF THE WORLD PROBLEMS AND PRESENT TRENDS IN MANAGEMENT

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Views regarding present-day therapy in pulmonary tuberculosis differ somewhat in this country and different parts of the world. The following quotation from a statement by the Committee on Therapy, American Trudeau Society, is an excellent pointer to the outlook one should develop: "The principal change that has occurred in the attitude towards therapy of tuberculosis in the past several years has been a loss of complacency; a change in the sense of satisfaction in achieving excellent results in 70 to 90 per cent. of cases even in the face of advanced disease, to a sense of dissatisfaction with the 10 to 30 per cent. of treatment failures. There is now a striving to achieve 100 per cent. good results in treatment through the better or more intelligent use of the drugs we now have." In other words, it would be well worth our while to pay greater attention to our failures and to seek an explanation as well as a solution for these problems. Such failures would only provide an unlimited reservoir of infection and thus delay the eventual eradication of tuberculosis.

Antimicrobial Therapy

Treatment results between countries vary, and this also applies between states in this country. Thus in the United States some centres have been reporting a much smaller percentage of failures than others. The British Medical Research Council trials (1955) on the chemotherapy of tuberculosis are not perhaps as widely known outside British Commonwealth countries as they could have been. It was recommended, as a result of those trials, that daily streptomycin with daily isoniazid was the best therapeutic combination. These findings have since been confirmed by others in this country such as National Jewish Hospital, Denver, who also supplied important modifications to such a regimen. These ideas were not widely accepted in the United States, where tuberculosis therapy apparently received a tremendous impact from the Veterans Administration trials also carried out about the same period. These trials recommended daily INH with PAS as the optimum treatment. However, as Wier (1953) points out, the V.A. trials had not as yet included any regimen with daily streptomycin. Thus with some exceptions there has been and still is a widespread use of either daily INH with PAS, or daily INH with intermittent streptomycin, in the *initial* treatment of most cases of pulmonary tuberculosis.

Great emphasis has been placed on the importance of the right choice of

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initial therapy, and with present-day knowledge one has to admit that *inadequate* initial therapy had been the cause of the substantial number of treatment failures seen today. Certainly many of these could have been avoided. Kass *et al.* (1957) have analysed the figures from the V.A. trials thus: sputum conversion at 5-8 months of treatment was achieved in 85 per cent. of cases treated with daily INH and PAS; in 68 per cent. of those treated with intermittent streptomycin and daily INH; in 58 per cent. of those treated with intermittent SM and daily PAS. The authors' figures showed close to 100 per cent. sputum conversion in previously untreated cases, using daily streptomycin—high isoniazid combination. PAS was used in certain cases to raise the level of the microbiologically active serum INH. A similar trial at this hospital (Saliba and Beatty, 1959) on previously untreated patients with moderately to far advanced pulmonary tuberculosis has also resulted in a 100 per cent. sputum conversion by six months of such a high dosage treatment regimen. On the other hand, a random group of patients treated medically and surgically between 1955 and 1956 was also analysed. The medical treatment consisted of daily INH with PAS, or intermittent SM with daily INH; surgery was also carried out in about two-thirds of the cases. This group showed a failure of the sputum to convert in 30 per cent. of the cases in spite of many months of chemotherapy (Saliba and Beatty, 1959).

This method of high dosage treatment is not widely popular in the United States as yet, although a few centres, notably the Denver group, have used this method for a few years and have reported excellent results (Russell *et al.*, 1958 and 1959; Mitchell and Bell, 1958). Nevertheless other less potent regimens are still extensively used here in initial treatment (Saliba *et al.*, 1959). One often hears the argument that a major drug has been withheld for future developments, such as surgery. One can counter this by stating that better initial therapy has been shown to produce better results and a higher percentage of sputum conversion; the surgical risks are then also decreased.

Some of the Recent Advances

The number of antimicrobial agents available steadily increases. Thus, besides the original drug trio of SM, INH, PAS, also the most effective, one has seen the use of such combinations as Viomycin with Oxytetracycline, and in the last few years Pyrazinamide and Cycloserine. More recently, Kanamyscin and Thiocarbanidin were introduced. Reports in the literature on the newer agents have shown some encouraging results in retreatment cases, from Toguri and Atwell (1958) and Ritchie and others (1958). Hand in hand with this advance in therapeutic measures has come a greater demand on our laboratories. The importance of drug susceptibility studies is well established, though one still finds centres where such examinations are not done. This subject was discussed at a Paris symposium held in 1957 by the Committee of the International Union against Tuberculosis. Divergent views were presented but the consensus of opinion favoured such studies, and regarded the emergence of resistant strains of tubercle bacilli as highly significant.

Catalase and peroxidase activity studies and the early recognition of anonymous mycobacteria are playing a definite role. Finally, some more privileged centres have regular serum INH and SM determinations as a guide to the correct dosage to be used in the individual patient. It has been amply demonstrated by Mandel and others (1957) and Biehl (1957) that approximately 45 per cent. of the population are rapid inactivators of INH, *i.e.* achieve a serum level of the microbiologically active drug of less than 0·4 mcg./ml. Some of these are classified as very rapid inactivators and achieve a level below 0·2 mcg./ml. Morse and others (1956) and Saliba (1958) believe that these usually require the addition of PAS to raise the serum INH level.

The theory of choice today is that drug resistance is a matter of selection rather than adaptation. Thus in a large population of tubercle bacilli 1 in 10^6 is thought to possess inherent resistance to streptomycin; 1 in 5×10^4 inherent resistance to INH, the latter being more common (Storey *et al.*, 1959); Cohn *et al.*, 1954). On the other hand, Cohn *et al.* (1959) showed that not 1 cell in 10 billion is a mutant resistant to both drugs inherently. Thus to render sputum negative it is essential to deliver at least two drugs in *adequate* quantities. It is thought that double resistant mutants possibly do exist if one examines a large enough population of bacilli. It is theorised that such cases could then provide the occasional treatment failure even on a high dosage regimen. In these instances adequate treatment with three drugs would be indicated. From the practical standpoint, if one delivered INH in adequate dosage and SM inadequately, then INH resistant mutants would be selected first. Similarly, a combination of adequate SM and inadequate INH would select SM resistant mutants first. If both drugs are administered in *inadequate* quantities then a lack of antimicrobial effect may be noted and the bacilli may well remain drug susceptible. However, if the choice of therapy is appropriate and adequate regarding dosage, then excellent results with sputum conversion should be obtained in practically all cases.

The surgical approach in treating pulmonary tuberculosis may have reached its peak. Recently one has noticed a decrease in the number of surgical beds in some parts of the world. Medical therapy has developed at a rapid pace, so that the newer methods of combined chemotherapy may promise actual sterilisation of tuberculous foci. Indeed, some authors believe that residual lesions or cavitation, "open negative cases," need no longer indicate surgery in every instance, provided chemotherapy is continued for a long period. Reports are seen increasingly of resected specimens showing no evidence of viable tubercle bacilli (Heaton *et al.*, 1959, Eilson *et al.*, 1958, and Mitchell *et al.*, 1959).

Discussion

The introduction of drugs has already produced remarkable results in the morbidity and particularly in the mortality from tuberculosis all over the world. Prior to the chemotherapy era a decline in mortality was already noted, and this was interpreted by some as heralding the defeat of tuberculosis. This decline has assumed greater proportions since the introduction of specific

antimicrobial agents. It is true that in many countries tuberculosis still presents a major problem, the main contributing factors being economic instability, a low standard of living with poor nutrition and overcrowding, and low standards of education and hygiene, in contrast with the status in many western countries.

It has been estimated that tuberculosis in India kills one person every minute, or about 500,000 deaths per year. The incidence being 6·6/1,000 population, India would have about 2½ million active cases of tuberculosis. Hospital and other facilities are inadequate; in 1954, for instance, the tuberculosis bed capacity was 16,827. Much has been done with regard to case finding, BCG vaccination, treatment, etc.; much needs to be done. In Formosa the position is not so bad, but again treatment is carried out to a large extent on a domiciliary basis because of lack of hospital facilities. Multiple drug therapy has been the exception rather than the rule, and only in 1959 was it planned to start multiple drug therapy on a domiciliary basis (T'Ao, 1959).

Dormer (1958) discusses some of the problems from tuberculosis in the tropics. He states that at the age of 10 years 50 per cent. of the population are already tuberculin positive. Overcrowding predisposes to rapid spread of infection and primary disease is also rapidly progressive. Adult disease is usually fulminating and secondary invading organisms add further to the complications. Here also INH is often used as single drug therapy. Similar problems are emphasised in a tuberculosis report on the South Pacific areas. In the British Solomon Islands Protectorate a survey suggested an incidence of 3,000 cases of active tuberculosis (pop. 109,000). A mass X-ray survey in Netherlands New Guinea in 1958 showed a tuberculosis morbidity rate of 40 per thousand. In the Territories of Papua and New Guinea hospital figures for 1956-57 showed a tuberculosis mortality rate of 13 per cent.; the infection rate increased with urbanisation and contact with Europeans. In the kingdom of Tonga it was rare for patients to seek early hospital treatment, for tuberculosis is still treated as a terrible scourge and patients conceal their symptoms as long as possible. A report on Guam gives a contrasting figure. It is stated that here patients display a rapid and lasting regression of pulmonary lesions after three to four months of drug therapy. They have not recorded a single relapse in five years' follow-up. If this rosy picture could also apply to similar countries, many of the world tuberculosis problems would be greatly simplified.

Domiciliary care, single drug therapy in many instances and BCG vaccination play a major role in the countries referred to in the preceding paragraphs. By present-day knowledge the drug therapy carried out under the conditions is probably inadequate in many instances. Immediate results are good, but one wonders if relapses discovered in the future may not be found excreting drug-resistant tubercle bacilli. The outlook would then be just as serious, if no other powerful anti-tuberculous agents have been added to our armamentarium.

At the other end of the scale we have reports from many western countries such as Britain, Sweden, Denmark, Australia, Canada and U.S.A. These reports have been most encouraging and comparative figures for morbidity

and mortality during the past decade are seen in Table I. N. Ireland and Scotland show the highest decrease in mortality, the figures being 81·0 and 81·5 per cent. respectively. According to the NAPT, the N.T.A., and Hedvall (1951 and 1958), the available hospital beds in these countries have been adequate for the past several years. Hospital facilities are inadequate precisely in those countries where tuberculosis is a major problem. Thus in 1955 Japan had 122,967 tuberculosis beds, and in the same period newly diagnosed cases amounted to 517,477. Colombia in 1957 had 2,777 beds when 13,143 new cases were found. Comparative figures for Hong Kong in 1955 were 473 beds and 14,148 new cases. These are but a few examples (Table II).

TABLE I.—TEN-YEAR SURVEY OF MORBIDITY AND MORTALITY FROM TUBERCULOSIS:* SELECTED COUNTRIES

Country	*1948/1949*		*1953/1954*		*1957/1958*		*Per cent. decrease in mortality (ten-year period)*
	TB New cases	*Deaths/ 100,000*	*TB New cases*	*Deaths/ 100,000*	*TB New cases*	*Deaths/ 100,000*	
Argentina	—	57·0	14,701	40·0	14,554	—	—
Australia	3,884	24·8	4,979	11·0	3,948 (1956)	5·4	78·2%
Austria	—	88·0	7,871	34·0	6,141	27·0 (1956)	58·9%
Belgium	—	55·0	7,013	29·0	5,922	23·0	58·2%
Canada	12,021	27·2	9,734	10·1	7,502	5·2 (1956)	80·8%
Ceylon	—	57·0	4,610	30·0	4,836	19·0	66·6%
Colombia	—	—	13,559	26·0	13,143 (1956)	27·0	—
Denmark	—	25·0	1,983	9·0	1,288 (1956)	5·0	80·0%
Egypt	—	43·0	7,132	29·0	6,655	—	—
England and Wales	43,971	40·5	40,917	17·9	28,870	8·9	78·2%
Formosa	—	156·9	—	61·4	72,525	54·2	65·5%
France	—	74·0	60,074	37·0	—	27·0	63·5%
Germany Fed. Rep.	—	67·0	107,538	22·0	80,128	19·0	71·6%
Hong Kong ..	—	—	11,900	131·0	13,665	103·0	—
Hungary	—	—	35,483	44·0	27,980	34·0	—
Ireland	—	104·0	6,602	40·0	—	24·0	76·9%
Italy	—	62·0	70,948	24·0	— (1956)	21·0	66·1%
Japan	—	179·0	507,244	67·0	518,142 (1956)	47·0	73·7%
New Zealand ..	—	—	1,439	17·0	1,190	11·0	—
Northern Ireland ..	—	69·0	1,651	23·0	1,155 (1956)	13·0 (1956)	81·0%
Norway	—	51·0	2,156	16·0	1,694	10·0	80·0%
Scotland	—	76·0	8,844	26·0	8,565	14·0	81·5%
Sweden	7,933	41·0	4,991	15·0	3,445	8·0	80·4%
Switzerland ..	—	53·0	7,488	23·0	5,811	18·0	66·0%
U.S.A.	145,131	30·0	106,925	12·3	86,861	7·8	74·0%

* 1. Representative years of 1949, 1953, 1958 were used when possible.
2. Non-respiratory tuberculosis was also excluded when feasible, though the figures are not appreciably altered.

In England all tuberculosis treatment, medical or surgical, is entirely free, whether on an in-patient or an out-patient basis. Welfare assistance and rehabilitation play an important part in this treatment. In Australia the position is fairly comparable, with the addition of a government pension for all persons over 16 who contract tuberculosis. Treatment is also free for all patients; and a patient may choose to be treated by a private physician and still be eligible to receive the necessary free drugs (Roche, 1958). Australia has also been carrying out case-finding programmes and BCG vaccination in Papua and New Guinea. Several sanatoria are under construction. Chemotherapy is extensively used, and special surgical teams visit the capital regularly when surgical programmes are carried out.

TABLE II.—RATED BED CAPACITY FOR TUBERCULOSIS: SELECTED COUNTRIES

Argentina	12,078 beds in 1955.
Australia	A decrease in the number of beds from 5,800 to 4,712 in 1958. Some further 1,500 expected to be given up in next few years.
Austria	7,132 beds in 1955.
Belgium	4,753 beds in 1955.
Canada	14,512 in 1958, a decrease of 4,000 over 1951. 78% occupied.
Ceylon	1,949 beds in 1955.
Colombia	2,777 beds in 1957.
Denmark	3,833 beds in 1955.
Egypt	6,137 beds in 1955.
El Salvador ..	688 beds in 1955.
England and Wales	A decrease from 31,273 in 1949 to 26,358 in 1957. Of the latter 20,085 were occupied.
Formosa	289 beds in 1956.
France	38,114 beds in 1955.
Germany (Rep.) ..	46,035 beds in 1955.
Hong Kong ..	473 beds in 1955.
Hungary	10,538 beds in 1955.
India	16,827 beds in 1954.
Ireland	5,401 beds in 1953.
N. Ireland ..	991 beds in 1955.
Italy	59,584 beds in 1954.
Japan	122,967 beds in 1955.
Mexico	1,921 beds in 1955.
New Zealand ..	1,582 beds in 1955.
Norway	4,128 beds in 1954.
Scotland	6,899 beds in 1955.
Sweden	A decrease from 8,454 in 1948 to 6,847 in 1957. About two-thirds occupied.
Switzerland ..	10,764 beds in 1953.
U.S.A.	A decrease from 103,000 in 1949 to 76,000 in 1957. State owned beds not appreciably reduced 1954-1957.

In the United States problems may vary from state to state. Tuberculosis beds can be under different control, *e.g.* State, Federal, Veterans, or private. Thus in some state-owned hospitals a patient pays according to his means. When discharged many patients are expected to buy their own drugs, and one wonders if treatment is then taken strictly as prescribed. Another problem is the head of a family with no children who may not be eligible for welfare assistance; unless he is otherwise insured this creates a serious problem for his dependants. All these factors may have a bearing on the against medical

advice discharge rate from tuberculosis hospitals in this country, which is about 30 per cent. It is the writer's impression that this figure is much higher than that experienced in other countries.

Summary

Probably the only reports on record showing approximately a 100 per cent. reversal of infectiousness are those resulting from a daily SM-high INH combination. A possible exception is two series of cases reported by Crofton (1958) and by Ross *et al.* (1958). Other methods of initial therapy in tuberculosis have consisted of various combinations of streptomycin, isoniazid, PAS, viomycin, cycloserine and pyrazinamide—all used in conventional doses. Results vary, but all report therapeutic failures ranging from 3 to 10 per cent. or more. When this is projected over the number of admissions throughout all the hospitals in a particular country the figure becomes high indeed; so that even a failure of 1 or 2 per cent. need not be accepted, if these can otherwise be avoided. We are now faced with a percentage of drug resistant tuberculous infections, and unless a more effective regimen in initial treatment is used more universally, then therapeutic failures are bound to continue to increase. Thoracic surgery on such cases has been shown to result in a higher incidence of complications and post-operative deaths. From the medical standpoint, newer antimicrobials have given hope to some but have proved disappointing to many. Thus there is a definite need for other good anti-tuberculous agents in the class of streptomycin and isoniazid.

Dublin in 1941 forecast a substantial elimination of tuberculosis by 1960 for the majority of the population of the United States. Rich wrote thus in 1944: " The disease that still kills more than twice as many individuals as any other single cause of death during this particularly productive and enjoyable period of life (15 to 44 years) can hardly be jubilantly regarded as nearly conquered." In a sense these thoughts expressed by Rich are applicable even today. Great strides have been taken in the treatment of tuberculosis and mortality figures have been greatly reduced. Nevertheless, considered on a world-wide basis tuberculosis remains a formidable problem. Less fortunate countries have hardly started on the road to progress. Adequate control in most western countries alone is only a partial solution to this problem. Air travel has greatly reduced distances, and more people each year use this mode of transport, so that opportunity for infection persists.

For the many countries that have much to achieve in tuberculosis control, a rapid development of better hospital facilities is essential. Adequate chemotherapy in hospital, as outlined in the preceding paragraphs, with or without surgery, would ensure a much better use of a limited number of beds, as sputum conversion has been shown to be consistent and rapid in almost all cases. Once in a non-infectious state most patients could then be managed on a domiciliary basis, thus considerably increasing patient turnover. It is highly desirable to maintain adequate chemotherapy even in home treatment, and under prevailing curcumstances the second best choice would be the use of

daily INH with PAS, remembering the better results obtained with dual drug therapy compared to the use of a single drug. In this instance high dosage INH (with pyridoxine) with PAS would ensure a smaller number of treatment failures; though the problem of toxicity has to be borne in mind. The use of intermittent streptomycin with another drug, or that of INH alone, would at best give a false sense of security. Success would be scored in a number of cases, but therapeutic failures would be many.

Compulsory yearly X-ray examination for the adult population (as in the case of Australia), and compulsory hospitalisation of the recalcitrant patient, are steps in the right direction. The question of BCG vaccination in certain groups needs to be established. BCG has been extensively used in Europe, S. America, India and other countries, and reports of benefits therefrom are many; but it has not been highly favoured in the United States. All these factors, together with a more intensive case-finding programme and a more adequate therapeutic approach, have to be considered before a successful control of tuberculosis can be accomplished. In the writer's opinion an ideal set-up for tuberculosis treatment is that seen in England: a country-wide distribution of chest clinics with corresponding chest units either in a sanatorium or, as is the present trend, in a general hospital, provides an excellent and totally free service with regard to case-finding, hospitalisation, and treatment, as well as subsequent out-patient follow-up care.

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AN ANALYSIS OF SOME RECENT WORK ON TUBERCULOSIS IN AFRICA

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Introduction

It has long been known that tuberculosis is one of the important diseases in Africa and many surveys have been made in which tuberculin tests, physical examination or X-ray examination have been used. These are not analysed in detail in this paper, but the general impression obtained from them is that workers throughout Africa have more and more been impressed with the extent and seriousness of the problem.

In the present paper I have taken these facts for granted, and have summarised some of the significant papers published in the last decade on the clinical forms of the disease, treatment and control. As elsewhere in the world, the discovery of effective chemotherapy has brightened the picture, but immense efforts will be needed before any feeling of satisfaction can be entertained.

Pathological and Clinical Findings

The opinion has often been expressed that Africans with pulmonary tuberculosis tend to show a type of disease which is more acute and less fibrous than the type commonly observed in Europe. The corollary to this has been the assumption that the Africans to some extent lack the innate power of resistance which Europeans have developed, perhaps as a result of natural selection acting on communities long affected by the disease. This view is expressed, for instance, by Jones (1949) and Braun (1953), both of whom base their opinion on autopsy records in Nigeria.

But the unqualified suggestion that innate racial potentialities are fundamentally responsible for the acute type of disease which is undoubtedly common in Africans is vigorously disputed, particularly by Dormer (1958) in South Africa, whose long and varied experience leads him to the belief that environmental factors are much more important than inherited tendencies—"Apart from the influence of minor though important factors such as age and sex, tuberculous disease is caused by environmental stresses acting on infected individuals." These stresses arise from malnutrition, fatigue, crowding, and diseases engendered by poor hygiene. In this opinion Dormer is supported by Schneider (1954), and by Altmann (1950) who makes the point that whatever the respective merits of the genetic and environmental factors, the environmental are obviously important and can be changed.

Dormer's opinion is also supported by Stott (1950) in Kenya, who observed the course of the disease in prisoners, finding a relatively high death rate in

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Bantu, Nilotic and especially half-Hamite prisoners; the type of disease was usually acute and fulminating, suggesting overwhelming tuberculous septicæmia. Stott attributes this high death rate largely to the heavy physical work involved in the prison " hard labour " sentences, and to some extent the overcrowding which has taken place in the prisons. Diet on the whole was good, though not so rich in protein as the half-Hamites are accustomed to. It is relevant that Marche and Gounelle (1950) lay great stress on the importance of animal protein in the diet, and claim that deficiency in this is the determining factor in African tuberculosis.

The disastrous effect of tuberculosis is most evident in the African populations of cities to which they have been attracted by the prospect of work, and where so often they live in slums and shanty towns with all the disabilities Dormer mentions. In the organised industries such as the gold mining industry of South Africa, where the workmen are carefully selected, well fed and housed, the incidence is relatively low; the danger is in the unorganised communities attracted to the industrial scene, in which the worst features of the European industrial revolution may be repeated. Here the incidence may be as much as thirty times as high as in the European residents of the same cities. But the situation is very different in the rural areas where, in what Lyle Cummins once described as " the magnificent leisure of the African village," the more benign type of disease recorded by Davies (1951) in Tanganyika, Stott and Brass (1955) in Kenya, and Goodall (1955) in Nyasaland, is seen in a substantial minority of cases. The same is true of Zanzibar (Young, 1955).

Pulmonary tuberculosis is the common and epidemiologically dangerous form of the disease, but the non-pulmonary forms such as bone and joint disease are constantly encountered, though to a lesser extent. Glandular tuberculosis has received considerable attention. In Nigeria, for instance, Braun (1953) reports thoracic or abdominal glandular involvement in almost two-thirds of 330 autopsies on African adults, and in all of 310 children. The high incidence of abdominal glands suggests ingestion as the route of infection, but the actual process is not clear. Jelliffe (1949) and Jones (1951) in Nigeria comment on the frequency of tuberculous adenitis (commonly cervical, but also axillary and inguinal) in African children, and Keen (1953) reports to the same effect in South Africa. Inhalation may be the usual route of this infection in countries where milk is not a serious danger, but Jones remarks that the common food bowl cannot be ruled out.

In Eritrea Ferro-Luzzi (1950) describes a rapidly progressive diffuse nodular lympho-hæmatogenous tuberculosis, distinct from miliary disease, in which the mesenteric glands, peritoneum, spleen, liver and kidneys are affected, and which is rapid and invariably fatal. This occurs in both children and adults.

Treatment

In the last decade chemotherapy has been increasingly brought to Africa. In general the reports have been favourable, and two British investigations, conducted with all the care and impartiality characteristic of Medical Research

Council enquiries, have added precision to the general favourable opinion reached in many parts. Fox *et al.* (1956) compared the results of treatment with streptomycin+isoniazid, or PAS+isoniazid, on comparable groups of African patients in Uganda and British patients in England, all with acute, rapidly progressive disease; on short-term observation after 3-6 months of treatment there were no important differences. Most of the patients became afebrile and sputum-negative, and in half there was X-ray improvement. Pepys (1958) reported careful trials of the usual drugs carried out by physicians at several centres in Uganda, Kenya and Tanganyika, which again showed that the Africans responded as well as Europeans in the short run. Isoniazid alone was not so satisfactory as isoniazid together with PAS or streptomycin, but the use of a sulphone with isoniazid was of no value. Even in the best circumstances, however, 10 per cent. of the patients developed tubercle bacilli resistant to isoniazid.

The results observed in these carefully controlled experiments are in general supported very widely throughout Africa, for instance in Uganda (Hutton, 1956; Hutton *et al.*, 1956), Central Africa (Turnbull, 1955; Fletcher and Paul, 1957), Egypt (Ibrahim *et al.*, 1955), Tripolitania (Lollini, 1955), Belgian Congo (Lalouel, 1956), French Equatorial Africa (Bouthillier, 1955).

Some workers have tried isoniazid alone, with considerable success (Ferro-Luzzi and Tomassi, 1952; Sharma, 1953), but there is a general warning that isoniazid resistance, in Africa as elsewhere, is likely to be serious.

The question arises how to administer these drugs in Africa, where special tuberculosis hospitals and dispensaries are as yet few and patients are numerous, and there seems to be a growing inclination to administer them on an out-patient basis, the patient (perhaps after a preliminary short stay in hospital) taking home a supply of PAS and isoniazid, or attending at the out-patient department for periodical injections of streptomycin if that is prescribed.

Lauckner (1955, 1956, 1959), writing after up to five years of experience of out-patient treatment in Nigeria, remarks on the good results which may be achieved without any improvement in housing or diet, and without bed rest. He has found that a régime of PAS with isoniazid, continued for six months, is capable of influencing the great majority of non-fibrotic lesions, and that a régime of these drugs with streptomycin may induce a satisfactory response in 90 per cent. of lesions of all types. He has now abandoned minor collapse therapy, and argues that the results of drug treatment alone (although the danger of resistance exists) are good enough for this to be regarded as a measure of prevention, and that only treatment which is of public health significance can be afforded.

In South Africa Tobias (1956) reports satisfactory results with ambulant treatment for Cape Coloured patients (but not for Africans), though Sachs (1956) comments on the fact that patients so treated remain a danger, and that if the environment is bad it is better to admit them to hospital.

An interesting and important point is brought up by Haynes (1958), who in Kenya observed 6 cases in which pellagra followed treatment with isoniazid; he therefore advocates extra vitamin B for African patients so treated, and in com-

munities in which undernutrition or malnutrition are fairly common this precaution seems apt.

Handley (1956) and Venator (1958) have used steroid hormones, with the usual drugs, and report striking success in patients with the acute forms of tuberculosis.

Cycloserine has been used by Bellidenty and Potier (1957), Rouan (1958) and Darras and Vanderhoeven (1958), mostly on patients with chronic forms of the disease, and they report some improvement in otherwise incurable disease, without serious side effects. Rouan, indeed, thinks it second only to isoniazid, and claims that it can render fit for surgery patients formerly regarded as incurable.

As in other areas, in Africa surgery has in recent years been increasingly used in conjunction with chemotherapy for the treatment of pulmonary tuberculosis, and the results are unexpectedly good. In Kenya Nevill and Nevill (1957) estimate cure in 80-90 per cent. of patients selected for resection in spite of a high rate of complications; in Dakar Raoult *et al.* (1955) obtained good or excellent results with collapse treatment of various kinds in 72 per cent.; in Casablanca Guy (1956) reports good results from similar treatment in cooperative patients such as the Jews; in Johannesburg Fatti, Crawshaw and Wilson (1950) report favourably on collapse treatment and more radical surgery in Africans in whom the disease was roughly similar to the usual type seen in Europeans, and in Durban the results reported by Joubert and Le Roux (1955) with resection are encouraging. Some of these authors, and Haynes (1955) in Kenya, use minor forms of collapse—pneumoperitoneum, pneumothorax, phrenic crush—as ancillaries to drug treatment. Pneumoperitoneum and pneumothorax were for many years used by Davies in Tanganyika before the days of chemotherapy.

Surgery is of course used for tuberculosis of bones and joints, and in a vivid and exhilarating paper Kirkaldy-Willis (1958) writes of successes achieved in the African orthopædic unit in Nairobi. He thinks that all these patients have had minor attacks of pulmonary tuberculosis, and he first gives them a period of rest, immobilisation and chemotherapy. But rest in bed can be overdone and he operates after two to three months, by which time the supremely important doctor-patient relationship has been established; real laughter is more important than the most carefully planned and executed operation. It is refreshing to see this stress on the emotional element in treatment, so often recognised in Europe but so rarely mentioned in Africa, and it is important to acknowledge the fact that treatment can hardly be expected to be successful if the patient is anxious about himself or his dependants. It is for this reason that the arrangements made in several places for the financial security of patients and families are so important. They may be made by governments for their employees, by private commercial firms, or by voluntary tuberculosis associations like the Aden Society for the Prevention of Tuberculosis, which was formed by interested members of the Arab, Hindu and Parsee communities encouraged and led by Cochrane (1949).

Immunisation

Immunisation with BCG has for many years been taken up with greatest enthusiasm in the French parts of Africa. The vaccine has been given by mouth, by scarification, or by injection. Foley and Parrot (1953), for instance, in Algeria, formerly gave it by mouth to children without preliminary tuberculin tests, and later changed to scarification. They observed that these methods did no harm even though many children must already have been positive to tuberculin, and they advocate the technique though they would not do so for countries with plentiful medical facilities. Scarification is sometimes carried out along with smallpox vaccination; but BCG should be repeated at intervals of three years. The method was approved by Sergent (1951).

Other workers proceeded in the more conventional way, first testing with tuberculin and then vaccinating those who failed to react. Thus in Tangier, Saenz and Saguès (1950) vaccinated 7,486, in Algeria the International Tuberculosis Campaign (1953) vaccinated over 1 million, and in Morocco Houel (1950) vaccinated 553,366 and Gaud and Ripoche (1952) over 1 million. Smaller numbers are reported from Tunisia and from Dakar.

In most of these campaigns the conversion rates were reasonably good, and the vaccine could therefore be regarded as satisfactory for creating the allergic state. Its protective value has largely been taken on trust, but there have been several serious attempts to assess it. The difficulties of deliberate and statistically satisfactory assessment of BCG are well enough known in Europe and America, where the necessary long-continued observation of the vaccinated and control populations is at least possible; in Africa these difficulties are enormously increased—populations are shifting, the people are largely illiterate, medical records are incomplete, doctors are few and diagnosis has not become so exact as in the West. It is most unlikely, therefore, that any large and validly controlled trial of BCG could be undertaken. Nevertheless, attempts have been made. Sergent *et al.* (1954) in Algeria vaccinated over 20,000 newly-born Moslem infants by mouth, leaving an equal number of unvaccinated controls; all were poor and all were observed for at least five years. Mortality in the non-vaccinated at each age was higher than in the vaccinated—the excess increasing steadily from 2 per cent. in the first year to 100 per cent. in the fifth. The difference can only have been due to BCG. In Bougie City, Algeria, Sarrouy and Babeau (1957) followed up 1,322 vaccinated and 1,753 unvaccinated children for 2 or more years and X-ray then showed pulmonary tuberculosis in 0·8 per cent. of the vaccinated and 2·8 per cent. of the controls; the authors conclude that a degree of protection is indicated. In Morocco Nicolas (1952) followed up over 2,000 vaccinated children and a group of controls for about two years; X-ray showed no infiltration and 0·4 per cent. of hilar enlargements in the vaccinated, compared with 0·04 per cent. infiltration and 0·73 per cent. of hilar enlargements in the controls. Similarly in Morocco Gaud (1954) vaccinated 867 tuberculin-negative children (with clear X-rays) and kept 812 similar children as controls; two years later X-ray showed evidence of tuberculosis in 1·3 per cent. and 4·6 per cent. respectively. These children were all from a community with a high tuberculosis death rate.

Credit must be given to these French workers for attempting this assessment in conditions of great difficulty; it would be hard to deny that the trend of the evidence is favourable to BCG, but it would be equally hard to believe that BCG can be more than a very partial means of control.

BCG has been used on a large scale in the Belgian Congo (Camphyn, 1952; Brou, 1954), and more experimentally in Kenya (Haynes and Stott, 1951; Stott, 1952), Northern Rhodesia (Briggs, 1955; Briggs and Smith, 1957) and Mauritius (Lavoipierre, 1952; Wagner, 1955). Some difficulties have been noted in obtaining satisfactory conversion rates, and the risks of exposure of the vaccine to bright light have been appreciated. The vole organism has also been used in Northern Rhodesia, but the results were poor (Greening, 1956).

Control

Chemotherapy has provided an exciting and rewarding opportunity for physicians to get the better of tuberculosis, and the decline in mortality from this disease in Europe and America, which was proceeding well enough in pre-chemotherapy days, has now become precipitous. It is a reasonable interpretation of the work of Lauckner in Nigeria that he hopes for a similar outcome there, but in South Africa Dormer (1958) is less optimistic. Present campaigns, he admits, are succeeding in advanced countries, but certainly not in countries basing their total tuberculosis campaigns on the provision of facilities for BCG, and on the recognition and treatment of the disease. He agrees that " find, isolate and treat " is a good enough slogan for the individual person suffering from the disease, but " feed, house and keep clean " is more important for the people as a whole, and he places his greatest emphasis on these fundamental public health measures which have been acknowledged for a century as essential requirements for the control not only of tuberculosis but of crowd diseases in general.

Much of a programme of this kind could be achieved by legislation to control the feeding of organised groups of employed persons, to regulate housing and to provide the means for cleanliness, and if one were to preach, one could take as a text the notion that it is the doctor's duty to insist that statesmen and commercial leaders must put such matters much higher than they do in their lists of priorities. Doctors, after all, see the end results of neglect of elementary sanitary precautions, and it is a recognised part of their duty to prevent them. They may, and should, provide the driving stimulus, but action itself must be taken by the administrators, who, like all other groups, may need hard prodding to see further than immediate economic advantage. Many years ago in India tuberculosis was described as a key disease in that it reflected the general standard of public health and economic status, and in that fundamental measures to reduce its incidence by improving standards of living and education would at the same time reduce the incidence of other great groups of illnesses. It would be disastrous if the attractions of new drugs and of BCG were to entice attention away from the more fundamental but more difficult measures of general economic and sanitary development.

In one sense it is unlikely that this will happen. Industrial development will

undoubtedly take place on a large scale in Africa, and the end results may be more total wealth and with this more possibility of healthy living—an end, perhaps, to the present widespread malnutrition which devastates so much of African childhood. But without strict governmental control, guided by advice from public health officers, it is at least possible that industrial development, by attracting young men away from their tribal areas, may lead (as it has already done) to the dismal slum shanty towns round the great cities, in which men without their families live in crowded rooms, paying high rents and subsisting on poor diets, and are open to all the respiratory, intestinal and venereal diseases which already ravage those places.

Great industrial institutions provide good accommodation for their men, but smaller industrial firms and all the individual ancillary services of large towns cannot do so; and without a strong and imaginative housing policy the slums will appear; and in slums there will be tuberculosis, though this disease may not be the greatest of the adverse results of an African industrial revolution. The point I am trying to make is that somebody must make sure that the African worker not only receives fair wages for his work, and works in acceptable industrial conditions, but also that he lives in surroundings which are healthy and dignified. I believe that it is the duty of a government to insist that local authorities and employers of labour between them provide for the off-duty comfort of their staffs.

These measures are implicit in the general recommendations made by the World Health Organization (1950), but they are not enough, and WHO recognises the need for the provision of diagnostic and therapeutic services on a large scale. At this point special mention may be made of the work of H. N. Davies, who since 1927 has built up on the slopes of Kilimanjaro a hospital and a chain of dispensaries which introduced to that relatively dense African population the notion that tuberculous could be treated successfully. This work was carried out for many years in the face of great physical difficulties—buildings were poor, beds and staff were too few, equipment was inadequate, and treatment before the days of chemotherapy was at best chancy. But when the new drugs became available the organisation already existed and was known, and the range and scope of treatment could be expanded at once. Smaller centres now exist at many places in Tanganyika, but there is no doubt that they owe much to the pioneer work done at Kibongoto by Davies.

In Kenya Haynes (1951) suggests the creation of a special staff for tuberculosis, with special hospitals, or wards in hospitals, to cope with the clinical side of the problem. Similar proposals are made for South Africa by Sykes (1950) and Lewis (1953), who add the idea of settlements where patients may live with their families and where rehabilitation may be attempted. One of the functions of settlements would be segregation of infected persons from the general community, in conditions acceptable to the patient and the family, where the patient can still feel important and useful to the community. Sykes emphasises the truth that cultural and social factors are of particular importance in Africa, where ancient beliefs are tenaciously held and where traditional customs must be taken seriously into account. Lewis remarks on the help that

can be given by voluntary bodies such as the South African Tuberculosis Association in supporting tuberculosis settlements; there is a large one near East London, and he attributes the recent decline in mortality in that city largely to the work of this settlement.

Cost is obviously a factor in the construction of hospitals or other institutions, but both Lewis (1953) and Dormer (1950) have experience of cheap but perfectly satisfactory buildings, and Dormer has successfully recruited African girls for training as nurses to staff the institutions. If domiciliary treatment proves as successful as it has done elsewhere, the total need for hospitals may not be as great as we thought.

Summary

1. A brief account is given of the clinical types of African tuberculosis; reports on treatment generally show a favourable reaction which has considerably altered the outlook for individual patients.

2. Although Africans tend to show the acute and severe forms of tuberculosis there is a lot of support for the idea that this is not so much a result of inherent susceptibility as of unfavourable environmental features. These can be changed, and it is argued that the soundest measures of control are those which are equally valid for other crowd diseases, and which largely depend on administrative action and economic and educational advancement.

3. BCG is increasingly being used in Africa and there is some evidence that, as elsewhere, it confers partial protection. The opinion is expressed that although it should not be withheld it is by no means the solution of the problem.

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TUBERCULOSIS OF THE MOUTH AND THROAT

WITH SPECIAL REFERENCE TO THE INCIDENCE AND MANAGEMENT SINCE THE INTRODUCTION OF CHEMOTHERAPY

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Tuberculosis of the mouth has always been uncommon and it usually affects the tongue in patients with advanced pulmonary tuberculosis. Since the introduction of Mass Miniature Radiography and of effective anti-tuberculous drugs opportunities for its development have rapidly decreased.

The purpose of this paper is to review the reported cases of oral tuberculosis which have been treated with antibiotics, and to describe six new cases. In addition, eight cases of tuberculosis of the tonsils are reported.

Case Reports

Case I. A man of 56 was found in 1958 to have an ulcer on his tongue during dental treatment. It was painless and he was unaware of it. The patient looked thin and unwell, had a hoarse voice and for ten years had had a productive cough and winter bronchitis. He was breathless on exertion and had a stiff and painful right shoulder so that he was unable to work. The ulcer was on the dorsum of the tongue at the junction of the anterior and posterior halves, just to the left of the midline (Fig. 1*); it was about 3 mm. across, with an angular outline, red, overhanging edges and slough on the floor. There was no induration and only slight tenderness. The patient was edentulous. The regional lymph nodes were not enlarged. Radiographs of the chest showed extensive nodular infiltration of both apices but no evidence of cavitation. Laryngoscopy showed chronic inflammatory changes, consistent with, but not diagnostic of, tuberculosis. Blood examination showed a normal blood picture with Hb 98 per cent. The Wassermann reaction was negative. Examination of a smear taken for cytological examination showed a number of Langhans-type giant cells (Fig. 2). Sections of a biopsy specimen showed non-caseating tubercle follicles; staining by Ziehl Neelsen's method showed scanty acid-fast bacilli, but no organisms were seen in, or cultured from, a smear from the ulcer. A specimen of sputum taken before treatment began showed *M. tuberculosis* on culture. The patient was given streptomycin 1 g. intramuscularly daily, PAS 12 g. daily and isoniazid 100 mg. three times a day. Healing of the ulcer and the biopsy wound began after the first week of treatment and was virtually complete six weeks later. Sputum culture was negative five weeks after treatment began. Chemotherapy is being continued.

Case II. A man of 51 complained in 1949 of ulceration of the right side of the tongue. The lesion was first noticed eight months previously as a small hard lump. The lump had occasionally caused a little discomfort but no pain, and had never interfered with eating. The patient had had pulmonary tuberculosis

* The figure numbers in the text refer to Plate I.

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since 1945. He had bilateral pneumothoraces and had remained well and at work. On the right edge of the tongue, 2 inches from the tip, there was a swelling ¼ inch in diameter. The swelling, which was not tender, was firm with indurated edges and was covered by normal mucous membrane, apart from some minute areas of shallow ulceration with a yellowish floor. The patient was edentulous and the regional lymph nodes were not enlarged. Radiographs of the chest showed an artificial pneumothorax with good collapse on each side. A biopsy of the tongue showed non-caseating tubercle follicles; staining by Ziehl-Neelsen showed a few acid-fast bacilli. No acid-fast bacilli were seen in three specimens of sputum. The patient was given 1 g. of streptomycin intramuscularly daily to a total of 40 G. A month later the tongue was soft and the lesion barely visible. The patient remained well until 1953, when he developed a small pleural effusion and the right AP was abandoned. The left AP was also abandoned in the same year. In 1954 chest X-rays showed increased infiltration in the left upper zone and the patient was admitted to hospital, where he received a course of 60 G. of streptomycin. In 1956 the patient received a further course of streptomycin and recently his sputum has become positive for *M. tuberculosis* though his chest X-ray does not show any further deterioration. Throughout this time, that is almost ten years since he first had chemotherapy, the patient's tongue has remained normal and for most of this time he has been well enough to remain at work.

Case III. A man of 51 complained in 1950 of an ulcer on the right upper lip, which was painless and had been present about three months. The patient had had pulmonary tuberculosis since 1943 but now felt well and was at work. There was a punched-out ulcer about ¼ inch in diameter on the inner surface of the left upper lip. The edges of the ulcer were very firm and undermined. The floor was irregular and covered by yellowish slough. The regional lymph nodes were not enlarged. The patient was edentulous. Radiographs of the chest showed bilateral upper zone infiltration, more marked on the right side, with possible cavitation. The Wassermann reaction was negative. Clinically, the ulcer on the lip appeared to be malignant and was excised. Histological examination of the ulcer showed numerous tubercle follicles but no caseation. Healing of the lip was not delayed and no further treatment was given at this time. In June 1954 another ulcer occurred inside the right upper lip, though the patient remained otherwise well and there was no radiological evidence of any change in the pulmonary condition. Local treatment of the oral lesion with a PAS mouthwash (2 G. to the ounce) was tried and the patient used this conscientiously every two hours, keeping the solution in contact with the ulcer as long as possible. He remained at work and within a month healing of the ulcer had begun. By the end of August healing was complete and treatment was discontinued. The patient remained well until January 1956, when another ulcer developed under the upper lip. At this time, however, there was also evidence of renewed activity by the lung infection. The patient was given Dipasic 800 mg. daily and the ulcer healed within six weeks. The Dipasic was continued until the end of 1957 and the patient has remained well and at work since then. Throughout the years no tubercle bacilli have ever been detected in this patient's sputum by direct examination or culture.

Case IV. This woman of 34 reported in April 1958 with a history of a sore throat for seven months, with pain on swallowing for four months. She had a

cough as a result of the discomfort in the throat, but for only two or three days prior to admission. The patient felt unwell, had lost 2 stones in weight and was thin and pale. In the throat there was exudate and œdema, with two ulcers on the right posterior faux and some membrane. Examination of the chest, abdomen and central nervous system revealed no abnormal physical signs. The patient's temperature was 99·6° F., the pulse 100 and the B.P. 85/65. Radiographs of the chest showed confluent miliary mottling of both lung fields, more marked in the upper zones, with patchy shadowing of the apices and scattered elsewhere. No cavities were shown on the tomograms. Examination of the larynx showed no abnormality. The patient was treated by means of rest in bed, and with Dimycin 1 G., PAS 12 G. and isoniazid 400 mg. daily, together with oral iron and vitamin B complex. Progress was good and the throat healed rapidly. The sputum was positive on culture in May but became negative after June. The patient gained 3 stones in weight while in hospital and was discharged after four and a half months to continue with a daily dosage of 12 G. PAS and 400 mg. isoniazid together with vitamin B. A year after being first seen the patient was still well; chemotherapy is being continued.

Case V. A girl of 23 was referred by a dental surgeon in June 1957 for treatment of what was thought clinically to be a dental cyst. The patient was otherwise well. There was a firm rounded swelling, 1 cm. in diameter, in the buccal sulcus in the right premolar region. There was no pain or tenderness, the adjacent teeth were sound and there were no radiological signs of bony changes. In October 1947 the lesion, which had slowly increased in size and had become slightly painful, was curetted under general anæsthesia. Sections of the curettings showed chronic inflammatory changes but no specific features. The operation wound failed to heal, remained painful and continued to discharge for a month after operation. The lesion healed slowly during the subsequent months, but in January 1958 a tender swelling was still present and some small glands were felt in the right submandibular region. Histological examination of the rest of the tissue excised three months previously showed caseating tubercle follicles. No acid-fast bacilli were seen in specimens stained by Ziehl-Neelsen's method. Radiographs of the chest showed only calcified lesions at the hilum. The Mantoux reaction was strongly positive at 1 in 10,000 with transient symptoms and, according to the patient, discharge from the oral lesion. No discharge or sinus was visible twenty-four hours later, however. There was no family history of tuberculosis but the patient had been in contact with four friends who had been treated for pulmonary tuberculosis, and another who had tuberculous cervical lymphadenitis. The patient was given PAS 12 G., and isoniazid 300 mg. daily for three months. She remained well and at work and had no loss of weight from the time when she was first seen. In September 1958 and in April 1959 the patient was seen again; the oral lesion had remained healed and the patient's general condition was unchanged.

Case VI. A man of 44 complained in 1956 of an ulcer of the lower lip of about two weeks' duration. The ulcer was gradually increasing in size and was a little sore. The patient was otherwise well. He had had lupus vulgaris of the pharynx in 1938, of the nasal mucous membrane, naso-pharynx and hard palate in 1941, and of the lower lip in 1952. There was an ulcer 1·5 cm. by 1 cm. on the mucous surface of the left lower lip. The floor was dull and yellowish, the edge irregular and the base indurated. No lymph nodes were palpable in

the neck. The rest of the mouth was normal, apart from some scarring of the anterior part of the hard palate. There were no other abnormal physical signs and radiographs of the chest showed scarring and calcification in the left apex from an old tuberculous infection; there was no evidence of active disease. The ulcer on the lip appeared to be malignant, so that a wedge excision was carried out. Sections showed non-caseating tubercle follicles in the floor of the ulcer and in the sub-mucosal connective tissue of the buccal surface of the lip; there was no evidence of malignancy. The patient was given a short course of streptomycin and the lip healed rapidly.

Tuberculosis of the Tonsils

Eight cases have been seen in the past ten years and occurred in children between the ages of 2 and 10, four of them being under 5. In all cases the tonsils were enlarged and infected. In seven of the cases the cervical lymph nodes were enlarged, and this was the chief complaint. In the remaining case, a child of 3, there was pain and swelling of the ankle. Radiographs showed osteoporosis of the affected bones; the lung fields were clear. Tonsillectomy was carried out; sections showed tubercle follicles and culture was positive.

Discussion

The following varieties of tuberculosis of the mouth and throat may be seen:

1. Primary tuberculosis of the oral mucous membrane.
2. Primary tuberculosis of the tonsils.
3. Lesions of the oral mucous membrane, usually ulcers of the tongue, associated with pulmonary tuberculosis.
4. Infections of the bone around the teeth, or bone infections following dental extractions, associated with pulmonary tuberculosis.
5. Involvement of the oral mucous membrane by lupus vulgaris.

1. Primary Tuberculosis of the Oral Mucous Membrane

A case, diagnosed as primary tuberculosis of the oral mucous membrane in a woman of 29, was reported by Weber (1907), but pulmonary tuberculosis cannot be excluded. Since this paper sporadic cases have been reported and some of these are discussed by Brand and Ballard (1951). Since the introduction of chemotherapy 9 patients with primary oral tuberculosis have been reported in this country by Brand and Ballard (1951) 1 case, Galloway and Horne (1953) 1 case, and Boyes *et al.* (1956) 7 cases. During this same period it will be seen that only 2 cases of oral lesions secondary to pulmonary tuberculosis were reported from this country. Since, according to the geographical area and to the method of testing, 11 per cent. to 40 per cent. of children have a positive Mantoux reaction by the age of 13 (Pollack, 1957), it is probable that a number of primary oral lesions are overlooked because of their inconspicuous nature. No cases of primary oral tuberculosis appear to have been reported from America in recent years.

The nine oral lesions, described by the writers already mentioned, occurred between the ages of 2 and 17, and were painless indolent ulcers on the gums

accompanied by enlargement of the cervical lymph nodes. The Mantoux reaction was positive and the lesions failed to respond to local treatment. Case IV of the present series is unusual in that there was no ulceration and the regional lymph nodes were not enlarged until secondary infection by other organisms had followed operative interference. The presence of calcified hilar lymph nodes suggests that the oral lesion was a second (reinfection) primary.

The oral lesion in these cases heals eventually and, according to Boyes *et al.* (1956), may leave no scar. The importance of this oral lesion is in the complications to which the infection can give rise. Thus, in all the cases reported by Boyes *et al.* (1956), which are the only reported cases followed for more than a few months, caseation of the cervical lymph nodes occurred and required incision or dissection. One of the cases reported by these writers developed tuberculous meningitis and Brand and Ballard (1951) quote 7 other reported cases.

Treatment

There is now fairly general agreement that primary tuberculosis should be treated with chemotherapy; such difference of opinion as exists centres upon the prognosis, which is often good but which is unpredictable when the lesion is discovered. Infants and young children should always be treated whatever latitude may be allowed in the management of the older child. Primary oral tuberculosis seems to be prone to a high incidence of troublesome adenitis as a complication, so that it is logical to treat this form of the disease with combined chemotherapy, probably for up to two years or longer if necessary (Hoyle, 1959). Under such treatment hæmatogenous spread of the infection is very unlikely to occur and in addition, if treatment is begun sufficiently early, surgical treatment of the cervical lymph nodes may be avoided.

2. Primary Tuberculosis of the Tonsils

Among the surveys of the incidence of tuberculosis of the tonsils, Mitchell (1917), who also reviewed earlier work, found that of 106 children with tuberculous cervical lymphadenitis 38 per cent. had tuberculosis of the tonsils; of 100 children without signs of tuberculous lymphadenitis 9 per cent. were found to have tuberculosis of the tonsils. Ormerod (1939), from reports published during the previous eighteen years, found that not more than 2·35 per cent. of tonsils were tuberculous, but where there was tuberculous lymphadenitis the incidence of tuberculosis of the tonsils was between 35 and 55 per cent. In those patients with tuberculous cervical lymphadenitis in which the tonsils are not affected the site of entry of *M. tuberculosis* is speculative, but in some it is the oral mucous membrane, as already shown, and in others the skin of the face or head, as described by Miller (1953).

Diagnosis and Treatment

There are no characteristic clinical features of tuberculosis of the tonsils, and the diagnosis is only made after their removal and section. In the majority of cases, as in those reported here, the chief complaint is of enlarged cervical lymph nodes so that, in general, the diagnosis is made some considerable time after the

initial infection. It is likely, therefore, that surgical treatment of the lymph nodes will be unavoidable. The chief use of chemotherapy in these cases will be to prevent hæmatogenous spread of the infection, especially in the younger child.

3. Lesions of the Oral Mucous Membrane associated with Pulmonary Tuberculosis

This is the most important group because it is the most frequently reported type of lesion and because of the association with severe pulmonary disease.

Incidence

The many extensive surveys carried out during the period prior to the introduction of chemotherapy should give a reliable indication of the incidence of oral tuberculosis. These figures are summarised in Table I. The figures given by Farber *et al.* (1940) were obtained by reference to hospital records and the low incidence (0·1 per cent.) was, they suggested, due to incomplete examination of patients. The equally low incidence reported by Martin and Koepf (1938) refers to the more uncommon tuberculous lesions of the oral mucous membrane, other than the tongue. Thus, taking into account these variations, the average incidence of oral lesions among 33,039 patients with pulmonary tuberculosis was 0·2 per cent.

Table I.—Incidence of Oral Tuberculous Lesions in Patients with Pulmonary Tuberculosis

	Admissions for P.T.B.	*Oral tuberculous lesions*	*Incidence*
			Per cent.
Rubin (1927)	5,000	16	0·3
Martin and Koepf (1938)	3,835	5	0·13
Bryant (1939)	7,000	17	0·24
Farber *et al.* (1940) ..	9,000	9	0·1
Titche (1945)	8,204	30	0·36
	33,039	77	0·23

Completely at variance, however, with these findings are the frequently quoted conclusions of Katz (1941), who showed that in 200 autopsies carried out on patients dying from pulmonary tuberculosis lingual lesions occurred in 19·9 per cent. It would appear however that few of these lesions would have been detected clinically, both because of the situation of many of the lesions (87·3 per cent.) at the base of the tongue, and because more than half the lesions (54 per cent.) were either microscopic in size or were foci beneath an intact mucous membrane. Moreover, it is at least possible that a number of these lesions were terminal phenomena.

At the present time, since this type of lesion is usually associated with

TABLE II.—ORAL TUBERCULOSIS AND THE EFFECTS OF CHEMOTHERAPY

Author	*Age, Sex*	*Oral lesion site*	*Pulmonary lesion*	*M.tb. in sputum*	*Antibiotics: daily dosage of S, PAS, INAH*	*Duration of treatment*	*Healing of oral lesion*
1. Shamaskin (1947)	52 M	Tongue	Productive quiescent		2 G.	6 m.	3 m.
2.	57 M	Tongue	Predominantly productive		2 G.	4 m.	Relapsed.
3.	59 M	Tongue	Extensive bilateral progressive		2 G.	No response to treatment.	
4. Wolfer *et al.* (1948)	49 M	Tongue	Bilateral caseous cavitation +	+	1 G.	11 w.	11 w.
5. Schneider (1949)	55 M	Tongue	Bilateral caseous cavitation +	+	2 G.		1 m. almost complete.
6. Oppenheim *et al.* (1950)	51 M	Tongue	Far advanced bilateral cavitation	+	1 G.	4 m.	10 d. recurred.
7.	38 M	Tongue	Far advanced	+	1 G.	3 m.	4 w.
8.	54 M	Tongue	Far advanced bilateral	+	1 G.	3 w.	3 w.
9.	33 M	Cheek sinus	Far advanced bilateral	+	1 G. Tuberculous meningitis.	Died.	40 d.
10.	45 M	Angle of mouth	Bilateral caseous cavitation	+	1 G. 12 G.	4 m.	4 w.
11.	57 M	Gum	Bilateral caseous	+	Self-discharged.		
12. Mamlok *et al.* (1952)	61 M	Tongue	Extensive bilateral	+	1 G. 12 G. 0·6 G.		2 w.
13. Beales (1953)	45 M	Tongue	Cavity R. mid-zone	+	1 G.		Comfortable after 3 w., complete healing after aspiration.
14. Wiese (1953)	37 M	Tongue	Far advanced bilateral cavitation +	+	½ G. ½ G. 12 G.	6 w. 12 w.	Painless after 2 w.
15. Castigliano (1953)	78 M	Tongue	Bilateral fibroid. ?Cavitation		1 G.	10 w.	10 w.
16. Jenney *et al.* (1954)	28 M	Tongue	Far advanced		2 G. 12 G. 0·3 G. (p.w.)	4 m.	Healed 1 m.
17. Bruce (1954)	47 M	Gum	Active pulmonary and ileocæcal tuberculosis	+	Referred to sanatorium		

18. Oppenheim (1955)	60 M	Tongue and lip	Far advanced fibro ulcerative	+	1 G. 12 G.		28 d.
19.	32 M	Tongue	Far advanced bilateral cavitation	+	1 G. 12 G.		5 w.
20. Moore and Hamilton (1956)	50 M	Tongue	Widespread infiltration; fibrotic		Some PAS dose not specified		Excised.
21. Douglass and Foss (1957)	48 M	Tongue	Miliary	+	2 G. 20 G.	25 d.	20 d. painless, later healed completely.
22. Present cases I	56 M	Tongue	Extensive bilateral nodular infiltration	+	1 G. 12 G. 0·3 G.	Continuing	6 w.
23. II	51 M	Tongue	"Controlled" bilateral pneumo-thoraces	—	1 G.		1 m.
24. III	51 (1950) M	Lip	"Controlled" bilateral upper zone infiltration	—	Nil		Excised, normal healing.
	(1954) (2nd)	Lip	Unchanged	—	PAS mouthwashes		6 w.
	(1956) (3rd)	Lip	Renewed activity	—	Dipasic 800 mg.		6 w.
25. IV	34 F	Faux	Bilateral miliary	+	1 G. 12 G. 0·4 G.	Continuing.	Rapid improvement.
26. Oppenheim *et al.* (1950)	55 M	Alveolar bone	Far advanced bilateral	+	1 G. 12 G.	4 w.	2 m.
27.	54 M	Lower molar region	Far advanced	+	1 G.	6 w.	6 w.
28.	41 M	Lower molar region	Far advanced	+	1 G. 12 G.	8 w.	4 w.
29.	33 M	Upper incisor region	Far advanced	+	1 G. 12 G.	17 w.	4 w.
30.	54	Lower molar	Far advanced	+	1 G. 12 G.	120 d.	
31. Pekarsky (1954)	10 M	Mandible	Active, post-primary infection; spine and other bone infection	—	1 G. (every third day)		
32. Thilander and Wennström (1956)	39/56 M		Marked bilateral with cavitation	+	No treatment		Teeth extracted and swelling incised; normal healing.
33.	12 F	Lower incisors	Healing foci at apex. Osteitis of metacarpal		PAS dose not stated		Conservative treatment of tooth followed by healing.
34. Radden (1957)	33 M				INAH dose not stated		

advanced pulmonary disease, its frequency of occurrence would be expected to depend largely on the number of cases of pulmonary tuberculosis that have escaped early diagnosis and treatment, such as Case I. Since 1947 19 cases of oral tuberculosis of this type appear to have been reported from the United States. From the United Kingdom only 2 such cases appear to have been reported since 1949. All of the lesions (except Case IV) occurred in male patients and only five were less than 45 years of age. In contrast with these recent cases, only 3 of the 17 patients reported by Carmody (1915) were over 40.

Clinical Features

The tongue is the commonest site of the mucosal lesions, and Carmody (1915) in his review found that among 661 tuberculous lesions of the mouth reported since the early nineteenth century, 227 were on the tongue and 48 were on the lips. Ormerod (1939) in a period of fifteen years saw tuberculous involvement of the tongue in 20 patients, of the lips in 4, of the floor of the mouth in 3, of the gums in 2 and of the hard palate in 1. Of the recently recorded cases shown in Table II, and including the present cases, 18 involve the tongue, 2 the lip, 1 both the lip and the tongue, 1 the gum and 1 the cheek. Lesions of the gums, the buccal mucous membrane and the palate are reported by Martin and Koepf (1938), Bryant (1939) and more recently, Bruce (1954).

In general, then, most of the remarks made here refer to lesions of the tongue except where other sites are specifically mentioned. The common site is the edge of the tongue, particularly the anterior part (Ormerod, 1939; Titche, 1945). Ulceration is frequent, but Katz (1941) also described fissures, granulomata, tuberculomata and diffuse glossitis. Ormerod (1939) describes the ulcers as shallow, with granular floors and undermined edges, but there is great variation in the appearances described in the various reports. Pain is usually severe and Farber *et al.* (1940) consider it to be the outstanding feature and may be out of all proportion to the size of the lesion. As Cases I, II and III show, however, pain is not invariable.

Of the 25 cases summarised in Table II, 20 had extensive bilateral pulmonary lesions or " far advanced " disease. One case had unilateral pulmonary disease with cavitation, and in only 1 case (Shamaskin, 1947) among these earlier reports is the pulmonary disease described as quiescent. The occurrence of oral lesions in patients such as Cases II and III of the present series whose pulmonary infection is under control and who are in other respects well and able to work is exceptional. No positive sputa were obtained from either of these patients. The sputum findings are described in 22 of the other cases and all these were positive. The findings of Titche (1945) were similar.

Diagnosis

The most important aspects of this problem are to distinguish oral cancer from tuberculosis and to detect previously undiagnosed pulmonary tuberculosis. Even when the patient is known to have pulmonary tuberculosis a lingual ulcer is, on the basis of frequency, more likely to be carcinomatous. In both conditions a similar age group is affected and males predominate. Castigliano and

FIG. 1.—Ulcer of the tongue in a man of 56 with chronic pulmonary tuberculosis.

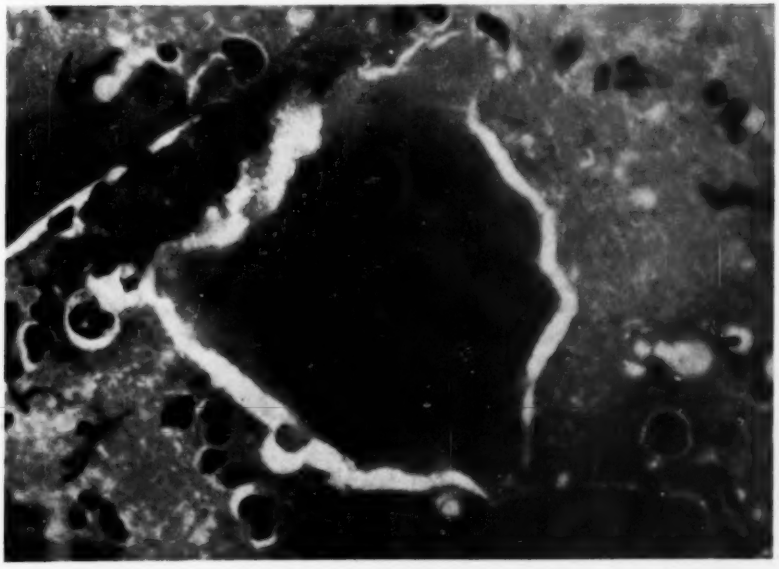

FIG. 2.—Smear from the ulcer of the tongue shown in the previous illustration showing a giant cell. (Hæmalum and Eosin. × 1,000.)

To face p. 48

Shigeoka (1953), for instance, saw only eight tuberculous oral lesions during a period in which they saw 2,200 cases of oral cancer. Further, in women of this age chronic ulceration of the mouth is even more likely to be malignant as oral tuberculosis in women is extremely rare, but the incidence of oral cancer is increasing. The main problem in the diagnosis of oral tuberculosis is the wide variation in the clinical features. None of the first 3 cases reported here showed the features usually expected and, on clinical grounds, were not considered likely to be tuberculous, even though 2 patients were known to have pulmonary tuberculosis. Moreover, tuberculous lesions, contrary to the usual conception, may show varying degrees of induration, as in the patients just mentioned, and in some described by Castigliano and Shigeoka (1953), Martin and Koepf (1938) and others.

It is therefore essential that all but the most transient lesions of the mouth should be examined by biopsy and there is no contra-indication to this measure. A frozen section or cytological examination of a smear from the lesion may give an immediate diagnosis. In Case I, for instance, a cytological examination showed giant cells compatible with tuberculosis.

Prognosis and Treatment

The finding of Katz (1941) that 93·6 per cent. of his cases had died within two years of the onset of lingual or laryngeal symptoms, though frequently quoted, is based solely on the autopsy findings and takes no account of any patients who may have recovered. But though, in the past, only a few patients with oral tuberculosis recovered, such as those reported by Titche (1945), the usual association of this condition with advanced pulmonary disease determined the poor prognosis. With regard to the more recent cases, Table II shows that only 2 of the 25 deteriorated during the period of observations, and these 2 received streptomycin only. In the majority of cases the periods of treatment and of observation were short, and though it is apparent that the oral lesion heals readily under systemic chemotherapy, these cases give no guide to present-day methods of treatment or to the prognosis to be expected. It is important to emphasise, therefore, that such patients as these must be given at least two antibiotics to prevent the development of resistant strains of *M. tuberculosis*, and such chemotherapy must be prolonged to prevent relapse. This has been shown by Hoyle *et al.* (1955), who also confirmed that chemotherapy can be safely continued for one or more years. In this series of 142 patients only 2 died of tuberculosis, while 126 were able to return to normal life with full activity. Ross *et al.* (1958) have shown that, apart from those patients who are already moribund on admission, deaths from tuberculosis occurred almost entirely in those whose infection was due to strains of *M. tuberculosis* resistant to several antibiotics. In this series of 305 patients, 20 (8·6 per cent.) died as a direct result of their infection. Of 63 patients in this series who received chemotherapy for eighteen months or longer, none relapsed. The prognosis of pulmonary tuberculosis today is therefore good, and there is no reason to assume that the prognosis of patients with oral tuberculosis is inferior. The statement of Castigliano and Shigeoka (1953), that the prognosis of oral tuber-

culosis is relatively poor while that of oral cancer in a patient with pulmonary tuberculosis is relatively good, is now no longer true. In fact oral cancer, the condition with which oral tuberculosis is most likely to be confused, has a poor prognosis and this is insufficiently widely appreciated. Cade and Lee (1957) have shown that, in a series of 461 patients with carcinoma of the tongue, only 27 per cent. overall survived for five or more years. The five-year survival rate is raised to 60 per cent., however, in the case of growths less than 2 cm. in diameter, and this forcibly emphasises the need for biopsy examination of oral lesions when they are first seen, whether or not the patient has pulmonary tuberculosis.

Since oral tuberculosis responds so well to systemic chemotherapy there is no indication for excision of the lesion as advised by Moore and Hamilton (1956). The statements of these same authors that oral tuberculosis occurs in early adult life, equally in either sex, and that the treatment is " indefinite " apply only to a past era. Where, on the other hand, as in Case III of the present series, the ulcer appears clinically to be malignant, excision-biopsy is a wise procedure. In the rare case of a tuberculoma of the tongue, as reported by Beales (1953), aspiration of the caseous material is obviously necessary.

4. Tuberculosis of the Bone around the Teeth, in Patients with Pulmonary Tuberculosis

Darlington and Salman (1937) reported and discussed 12 cases of this type. More recently Oppenheim *et al.* (1950) have described 5 cases, Thilander and Wennström (1956) 2, and Radden (1957) and Pekarsky (1954) 1 each. These are summarised in Table II. In addition, Cohen (1959) has reported a case of a cold abscess in the buccal sulcus in association with a rarefying osteitis of the jaw. These lesions cannot, in general, be distinguished from non-specific infections, such as chronic peri-apical granulomata or abscesses in relation to dead and infected teeth. Radiologically there is an area of rarefaction of bone, circumscribed or diffuse, or occasionally simulating a dental cyst, so that the specific nature of the infection is not apparent unless a biopsy examination is carried out. This is not likely to be done in the case of the smaller lesions, however, unless perhaps the patient is known to have pulmonary tuberculosis.

The common course of events is that the dental lesion is treated by extracting the affected teeth, but instead of healing, a persistent infection, sometimes with proliferation of granulation tissue from the socket, occurs. If this remains untreated, as in the case reported by Radden (1957), gross bone destruction may follow. If, however, histological examination of the inflamed tissue is carried out, the diagnosis becomes apparent and effective treatment can be instituted. Surprisingly perhaps, in 9 out of the 12 cases of this type described by Darlington and Salman (1937) the oral lesion healed after operative treatment alone. Moreover 6 of the 12 patients were alive at the end of the periods of observation varying from eight months to two and a half years.

With regard to the 6 recent cases, only 1 patient died during the period of observation. This child had tuberculosis of the lungs, the spine and other bones

and received streptomycin only (Pekarsky, 1954). In 7 of the other cases healing of the oral lesions occurred after surgery and chemotherapy. In 1 case, however (Thilander and Wennström, 1956), though the patient had advanced tuberculosis of the lungs and spine, the oral lesions healed after extraction of the affected teeth and excision of the swelling, without chemotherapy. The treatment of these cases of pulmonary tuberculosis complicated by dental infection is, however, as already described in relation to tuberculosis of the oral mucosa, prolonged systemic chemotherapy with several drugs. In addition, the usual surgical treatment for the oral lesions should be carried out.

5. Lupus Vulgaris of the Oral Cavity

According to Allen (1954), the mucous membrane of the mouth or larynx is involved in some 70 per cent. of cases of lupus. This figure is excessively high and Carmody (1915), writing in the days when lupus was relatively common and when involvement of the mucous membrane was more likely to occur owing to the inexorable spread of the disease, considered that oral lesions were rare and he had seen no examples of the disorder among his cases of oral tuberculosis. Carmody also quotes even earlier writers to the same effect, while, more recently, Ormerod (1939) considered lupus of the pharynx to be rare, and lupus of the mouth to be even more uncommon. Apart from the case of lupus of the lip (Case VI) no cases of lupus of the oral mucous membrane have been seen here during the past ten years and few cases have been reported from elsewhere. Single cases have been reported by Kanaguinis (1949), Russell *et al.* (1953), among a series of 15 patients with lupus of the skin, Dowling and Seville (1953) and Huriez and Pelce (1958), among a series of 211 patients with lupus of the skin. In all these the palate was the part of the oral cavity affected. In the case reported by Kanaguinis (1949) the naso-pharynx was also involved. Rasmussen (1954) described the effects of chemotherapy on 77 cases of lupus of the mucous membranes, but even of these, the oral mucous membrane was affected in only 1 case; the nasal cavity was the site affected in all the other cases, but in 2 the larynx and in 1 the pharynx and larynx were also involved. Thus, though it is possible that the mouth is not examined in all cases of lupus, so that some cases are missed, it is apparent that lupus of the oral mucous membrane is rare and is becoming even more rare as the incidence of lupus declines. The infrequent occurrence of new cases of lupus vulgaris of the skin is shown by the fact that, in a series of 111 cases reported by Russell and Thorne (1956), the average duration of the disease was 37 years.

Diagnosis

The oral lesions of lupus vulgaris are described by Ormerod (1939) as consisting of nodules, pinkish and translucent at first, but becoming greyish and more solid in appearance. These tubercles may be grouped together in large masses extending over a considerable area of mucous membrane. Ulceration is rare and pain is unusual; the main symptoms are a feeling of heat and stiffness, while loss of mobility of the soft palate may give rise to difficulty in swallowing.

Diagnosis will depend on the usual association with lupus of the skin and often with tuberculous lesions elsewhere, and upon biopsy examination.

Treatment

From the few cases of lupus of the mucous membranes reported, little information is available about the response of these lesions to chemotherapy. The skin lesions, however, respond to anti-tuberculous drugs, and especially to isoniazid. Thus, Russell and Thorne (1956) showed that of 103 patients with this disease who completed a course of treatment with isoniazid, the lesions cleared in 99. Isoniazid was given in a total dosage of 300 mg. daily and continued for at least three months after clinical evidence of clearance of the lesions. The course of chemotherapy, therefore, lasted for about a year in most cases. Huriez and Pelce (1958) also discuss the principles of treatment of tuberculosis of the skin on the basis of 400 cases, of which 211 were lupus vulgaris. These workers consider that isoniazid should be given in combination with other antibiotics and the action of these drugs should be completed by a prolonged and intensive course of calciferol. The dangers of hypercalcæmia and nephritis that may result from treatment with calciferol must not be ignored, however, and the value of this drug, in combination with the usual chemotherapeutic agents, is not proved. With regard to lupus of the mucous membrane of the mouth or throat the few reported cases, like other forms of oral tuberculosis, cleared rapidly with chemotherapy even though the course of treatment in most cases was short. Thus Kanaguinis (1949) gave 5 g. of streptomycin over a period of a week, Russell *et al.* (1953) gave isoniazid as did Dowling and Seville (1953). Rasmussen (1954) gave PAS or PAS and dihydrostreptomycin, while Huriez and Pelce (1958) gave the treatment already described. It must be concluded, however, that the treatment of lupus vulgaris, as of tuberculosis elsewhere, is prolonged chemotherapy with several antibiotics.

Summary

1. Four cases of oral tuberculosis occurring in patients with pulmonary tuberculosis, 1 of primary oral tuberculosis, 8 of tuberculosis of the tonsils, and 1 of lupus vulgaris of the lip, are described.

2. Thirty-four cases of oral tuberculosis associated with pulmonary tuberculosis are reviewed. With few exceptions these patients received chemotherapy, though only for a short period.

3. The features of the various types of tuberculosis of the mouth and throat, including lupus vulgaris, are discussed and the necessity for biopsy examination is emphasised.

4. Five of the cases reported here were followed up for periods of between one and ten years and, with the previous cases reviewed, these show that oral tuberculosis responds rapidly to chemotherapy, but the essential principles of treatment are that several antibiotics must be given, and chemotherapy should be prolonged, usually for eighteen months or more. Under these circumstances the danger of hæmatogenous spread from primary oral tuberculosis is much reduced, and the prognosis of those cases with pulmonary tuberculosis is good.

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INVOLVEMENT OF THE PULMONARY VEINS BY BRONCHOGENIC CARCINOMA

By K. F. W. Hinson and H. C. Nohl

From the London Chest Hospital

The frequent occurrence of distant hæmatogenous metastases after surgical excision of carcinoma of the bronchus is a frustrating experience. This dissemination can only occur when malignant infiltration of the pulmonary veins has taken place. This report is the outcome of investigations carried out in order to assess the modes of pulmonary vein invasion, its frequency and its bearing upon the prognosis after resection.

Willis (1953) considered that in three-quarters of his autopsy cases bloodstream dissemination had occurred. The distribution of such metastases was similar to that recorded by Galluzzi and Payne (1955). In this series of 741 cases who had died from a bronchial carcinoma the commonest sites were:

	Per cent.
Liver	39·3
Adrenals	33·5
Brain	25·7
Kidney	15·4
Bone	14·6

Only about one-quarter of fatal cases showed no macroscopic distant metastasis.

Siegert (1893) first described microscopic evidence of malignant involvement of the pulmonary vein. Malignant thrombi in the pulmonary veins were noted by Goldman (1897). Thrombosis in the pulmonary vein was found in 24 of 139 cases of the disease by Simpson (1929). Aylwin (1951), using as the criterion of vascular invasion " the permeation of malignant cells through all coats of the vessel at least as far as the intima," found such involvement in 40 per cent. of 58 resected specimens. He noted that careful dissection showed a higher incidence. Invasion was more common in the oat-celled than in the squamous-celled growths. Widespread metastases were present in 80 per cent. of those cases whose operative specimens had shown vascular involvement. Ballantyne *et al.* (1957), using a different criterion (the proliferation of malignant cells within the elastic lamina), reported vascular involvement in 88 per cent. of their 59 surgical specimens. They demonstrated invasion both of the artery and vein and from their table it would seem that the venous involvement was 69 per cent. Collier *et al.* (1957) also studied surgical specimens for evidence of blood vessel invasion. This was found in 71 per cent. of their cases. Vascular infiltration occurred in all (100 per cent.) of the undifferentiated growths, less frequently with the adenocarcinomata (80 per cent.), while with squamous-celled tumours the rate was 63 per cent. Most of their patients with vascular

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involvement died within two years and only 6 per cent. survived five years, as compared with a five-year survival of 75 per cent. of those without blood vessel invasion.

Methods and Results of Present Investigation

Dissection Technique and Results

In 211 pneumonectomy or lobectomy specimens, which had been resected for a bronchial carcinoma, the pulmonary veins were opened along their course and sections prepared if definite thrombosis or roughness of the intima in the region of the growth were found. The larger vessels were frequently only cuffed by growth so that they could be traced far into the tumour without the intima being involved. In these cases there was microscopic invasion of the perivascular lymphatics of the adventitia, sometimes with infiltration of the media. Such findings were disregarded. Employing Aylwin's criterion of involvement, it was possible to demonstrate pulmonary vein invasion in 34 per cent. of the specimens. The highest rate was in the oat-cell group (6 out of 10), whilst the squamous-celled tumour showed the least tendency (28·5 per cent.). The 211 specimens of lungs were then classified according to Salzer's classification as modified by Nohl (1956), which records the extent of the growth, the degree of lymph node involvement, and the presence or absence of venous infiltration. Table I shows that the greater the extent of the growth the more likely is venous involvement to occur.

Table I.—Extent of Primary Tumour related to Lymph Node Metastases and Venous Involvement in 211 Cases

Extent	*Total*	*Lymph node metastases*		*Venous involvement*	
		Number	*Per cent.*	*Number*	*Per cent.*
Group "A"*	77	51	66	15	19
Group "B"	83	56	67	26	31
Group "C"	51	42	82	32	63

*Group "A": Tumour limited to the lung.
Group "B": Tumour invading the pleura.
Group "C": Tumour invading the mediastinum or chest wall.

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During this investigation it seemed, however, probable that invasion of the vessels as a potential source of malignant emboli was likely to have taken place in the smaller, thinner walled branches which could not be traced by naked-eye dissection. In order to investigate this problem further a special injection method, based on a technique developed by Shillingford (1951), was employed to facilitate the identification of the smaller pulmonary veins.

Injection Technique and Results

Forty-three freshly resected lungs or lobes were flushed with saline through cannulæ in each branch of the pulmonary artery until the washings returning through the pulmonary vein were free from blood. A bismuth-gelatin mixture was then injected through cannulæ tied in each separate branch of the pulmonary vein. These were then tied off and 10 per cent. formal saline injected into the bronchi until the specimen had regained its size and shape. After fixation sections were cut in the usual way.

The injection mass was easily identifiable (Fig. 1).* The finding of Reisseisen and Sömmering (1808) that most of the bronchial veins enter the pulmonary veins was confirmed. Occasionally the material was present in the veins of attached lymph nodes and in one instance malignant involvement of such a vessel was observed.

Using this technique it was possible to demonstrate involvement of the tributaries of the pulmonary vein in 40 out of the 43 specimens, *i.e.* in 92 per cent. of the cases. It is, therefore, justifiable to assume that some infiltration occurs in all cases.

THE INFLUENCE OF PULMONARY VEIN INVASION ON SURVIVAL AFTER RESECTION

Previous reports of the survival of surgical cases after excision all suggest that the heaviest mortality occurs in the first eighteen months following operation (Gibbon *et al.*, 1953; Sellors, 1955; Bignall and Moon, 1955; Belcher, 1956; Gifford and Waddington, 1957). In order to evaluate the significance of vein invasion on the ultimate prognosis after resection, 132 of the classified cases were followed up for three years or more. From Fig. 2 it will be seen that the number of survivors whose pulmonary vein was shown to be involved by the dissection technique (V cases) falls more steeply than those in whom this invasion was not demonstrated (Non-V cases), the overall percentage of survival being 30 per cent. and 44·5 per cent. respectively. The mortality which may be expected in those patients who had involvement both of the pulmonary vein and the mediastinal lymph nodes (V 3 cases) is also represented. It has the steepest fall and the overall percentage of survival was only 19 per cent.

In this connection it should be noted that gross involvement of these nodes is related to vascular invasion, as direct extension to the pericardium and great vessels may follow.

Conclusion

Having shown that malignant infiltration of small branches of the pulmonary vein is present in all cases, this study suggests that only invasion of major branches which can be detected by the dissection technique has any bearing upon prognosis.

Summary

The methods and results of investigations into the frequency of pulmonary vein involvement by bronchogenic carcinoma are described. It is shown that

* This figure appears on Plate II.

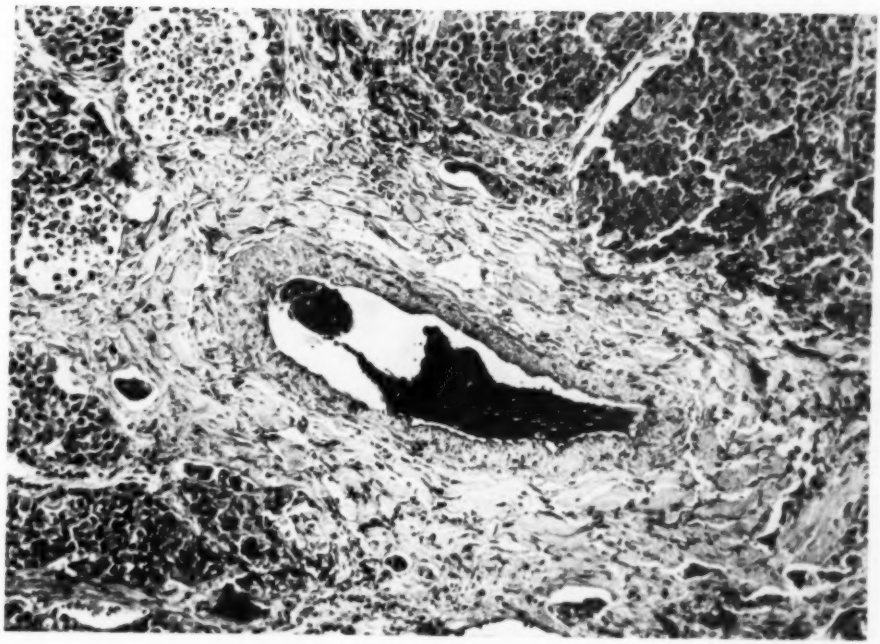

FIG. 1.—Microscopic section of a pulmonary vein containing a malignant thrombus. The dark bismuth-gelatine injection mass can also be seen in the lumen of the vessel.

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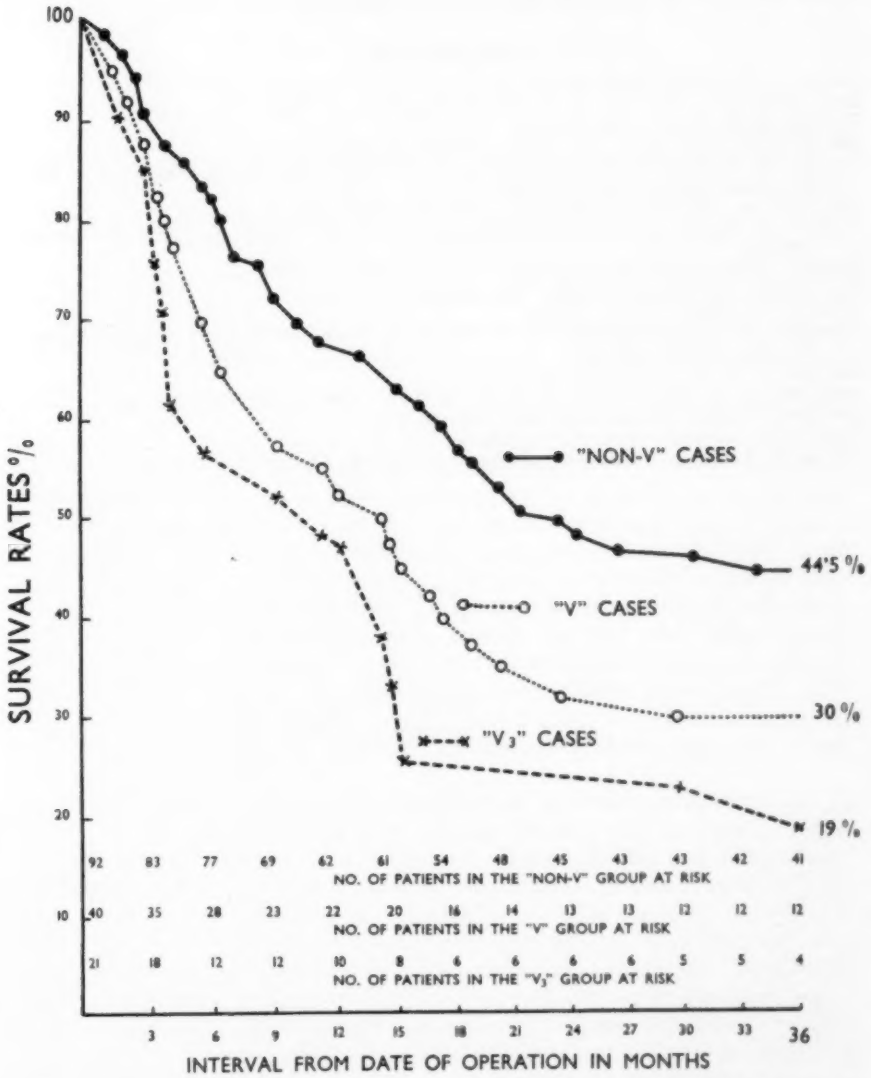
100
90
80
70
60
50
40
30
20
10
SURVIVAL RATES %
"NON-V" CASES
44'5 %
"V" CASES
30 %
"V3" CASES
19 %
92 83 77 69 62 61 54 48 45 43 43 42 41
NO. OF PATIENTS IN THE "NON-V" GROUP AT RISK
40 35 28 23 22 20 16 14 13 13 12 12 12
NO. OF PATIENTS IN THE "V" GROUP AT RISK
21 18 12 12 10 8 6 6 6 6 5 5 4
NO. OF PATIENTS IN THE "V3" GROUP AT RISK
3 6 9 12 15 18 21 24 27 30 33 36
INTERVAL FROM DATE OF OPERATION IN MONTHS

FIG. 2.—Survival rates of 132 patients followed up for three or more years, showing the influence of pulmonary vein invasion on prognosis after resection.

invasion of the small tributaries of the vein occurs in every case. A three-year follow-up after surgical excision, however, suggests that only infiltration of the major branches has any influence on the prognosis.

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PULMONARY MANIFESTATIONS OF HODGKIN'S DISEASE

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In addition to the lymph nodes, Hodgkin's disease affects organs containing lymphoid tissue, including the lung. Such lesions are frequently occult to clinical examination, but the use of radiography to detect mediastinal involvement makes them less likely to be overlooked in the lungs than elsewhere. Walton (1918) described pulmonary infiltration with hilar node disease as " giving the impression of a tuberculous process," and anticipated one of the main problems arising in cases with pulmonary involvement, which is to distinguish such lesions from secondary or coincidental disease such as tuberculosis, sarcoidosis, lung abscess, pneumonia, atelectasis and primary or secondary neoplasm.

The impression was current for many years, in the words of Hartfall (1932), that " the lung parenchyma is one of the less common situations in which the lesions of Lymphogranuloma, or Hodgkin's disease, may occur," but closer study of the incidence of pulmonary disease in this condition no longer supports this view. Versé (1931) found such lesions in 40 per cent. of cases of generalised Hodgkin's disease coming to autopsy, and Peirce *et al.* (1936) found radiographic evidence during life in 14 per cent. of 198 cases, many of these having been unsuspected clinically. In one-fifth of the pulmonary cases there was no evidence of mediastinal node disease. Jackson and Parker (1947) similarly found an incidence of 14 per cent. radiographically and 41 per cent. at autopsy. Other estimates have been 40 per cent. (Wolpaw *et al.*, 1944), 37·6 per cent. (Falconer and Leonard, 1936), 33 per cent. (Uddströmer, 1934), 29 per cent. (Sternberg, 1936), 15 per cent. (Kirklin and Hefke, 1931) and 12 per cent. (Gall and Mallory, 1942).

More recently, Levinson *et al.* (1957) showed pulmonary involvement in 37 per cent. of 91 patients, the sex ratio among the cases with lung lesions being identical with that of the series as a whole. Craver, Braund and Tyler (1941) found lesions in the lung more commonly in Hodgkin's disease than in lymphosarcoma or the leukæmias, with a radiographic incidence of 34 per cent. of nearly 300 cases, while 18 of 28 cases coming to autopsy were affected. The frequently reported difference in the incidence of pulmonary involvement found in life and at autopsy suggests that in many cases the lesions in the lungs appear late in the course of the disease; this is supported by the findings of Levinson *et al.* (1957) that the mean survivals of their patients from the onset of Hodgkin's disease and from the appearance of lung involvement respectively were 52 months and 13 months.

The patterns of lung disease in this condition are extremely variable in type, onset, progression and response to therapy, and their classification into sig-

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nificant categories is difficult. Ceelen and Rabinowitsch (1917) divided them simply into generalised and localised, while Wessler and Greene (1920) distinguished an infiltrative type, isolated nodules, and discrete nodules at the roots of the lungs. Lenk (1929) gave the following classification: (1) Hilar node involvement, occasionally penetrating the capsule and infiltrating the lung; (2) widespread small or large nodules, miliary or sub-miliary; (3) solitary or multiple large nodules, apparently arising from lymph nodes in the lung; and (4) bronchial mucosal lesions, resulting in stenosis. The last two forms are rare. Moolten (1934) made a comprehensive classification on the basis of his pathological studies, in which he had been impressed by the similarity of Hodgkin's disease, as expressed in the lung, to an inflammatory process. The terms used strongly reflect this and have not gained general currency.

Modification of a classification by Versé has been proposed by Sheinmel *et al.* (1950), and this is based on the presumptive method of entry and dissemination of the lesions within the lung (see Table I). It is certainly comprehensive but, in common with other attempts to classify this condition, its subdivisions are not mutually exclusive and on occasion it is difficult to apply clinically to individual cases. Here again it has proved difficult to relate prognostic factors or response to therapy to the various groups described.

TABLE I.—A CLASSIFICATION OF PULMONARY HODGKIN'S DISEASE

(By Sheinmel *et al.*, 1950, after Versé.)

I. Direct invasion of the lung in the presence of mediastinal node disease.

II. Peribronchial or endobronchial infiltrates in the presence of mediastinal node disease.

III. Massive homogeneous infiltrates—so-called " lobar infiltrates "—with varying degrees of mediastinal node disease.

IV. Lobular infiltrates with variable mediastinal node disease.
- (1) Punctate and/or mottled densities involving a variable segment or segments, usually basilar, on one or both sides.
- (2) Circumscribed nodular densities
  - (*a*) Solitary, isolated.
  - (*b*) Solitary, in the presence of extensive disease elsewhere in the pulmonary parenchyma.
  - (*c*) Multiple, diffuse, bilateral (ultimately coalescent).
- (3) Confluent irregular densities
  - (*a*) Solitary.
  - (*b*) Multiple.
  - (*c*) Widely disseminated (ultimately coalescent).

V. Generalised dissemination.
- (*a*) True miliary,
- (*b*) Lymphangitic spread.

It is evident, therefore, that pulmonary Hodgkin's disease is neither very uncommon nor simple in pattern. This paper presents the principal features of six illustrative cases in which pulmonary involvement was prominent and outlines the problems of diagnosis and management which were encountered.

Case Reports

Case 1. Diffuse Reticulation

D.E., a schoolboy, was first diagnosed as having Hodgkin's disease at the age of 10 years, when he presented with cervical, axillary and mediastinal lymphadenopathy and moderate splenomegaly. The diagnosis was confirmed by lymph node biopsy. At the age of 4½ years tuberculous cervical lymph nodes were excised, and further nodes were removed when he was 7. When the patient was 5, his father died of miliary tuberculosis, and later his sister succumbed to polyarteritis nodosa with pulmonary involvement.

A course of radiotherapy led to considerable improvement, but in 1949, at the age of 12, he came under the care of one of us (P.E.) complaining of fatigue, breathlessness and unproductive cough. He appeared anæmic but otherwise showed no physical signs and the blood count revealed a hypochromic anæmia with hæmoglobin 64 per cent., white cells 8,400 per cu. mm., and E.S.R. (Westergren) 71 mm. in one hour. Chest radiography showed hilar lymphadenopathy more marked on the right, and a diffuse, fine reticulation in all zones of the pulmonary fields sparing only the margins of the lungs. He improved with ferrous sulphate and no further specific therapy was given. His remission continued until 1952, when at the age of 15 he was found to have developed cervical, axillary and inguinal adenopathy, although he was symptom-free, gaining weight and not anæmic. The liver and spleen were just palpable, but the blood count and E.S.R. were normal, and the Mantoux reaction was negative with 1 : 100 O.T.

Shortly after this he was treated elsewhere for multiple warts, and the bilateral "streaky shadowing" observed in a chest X-ray, combined with paratracheal and parahilar lymphadenopathy revealed by tomography, were regarded as manifestations of sarcoidosis, from which, indeed, they could not by appearance alone be regarded as distinguishable. In October 1952 he was admitted to Dorking General Hospital under one of us (P.E.) and a cervical lymph node was removed for further biopsy. This was submitted to Dr. Gledhill, Dr. Hinson and Dr. Robb-Smith, all of whom concurred in a diagnosis of Hodgkin's disease. The chest radiograph at this time showed the pattern of reticulation in the lung fields to be much coarser than when previously observed (Fig. 1).* Radiotherapy was again given by Mr. Jackson Richmond to the neck and thorax with good effect.

In May 1953 he again complained of cough, and a chest X-ray showed bilateral hilar opacities with widespread, multiple small opacities in the lungs. The liver and spleen had further enlarged. A course of triethylene melamine had a satisfactory response, but a further exacerbation in September 1953 did not respond to similar treatment, and he lost weight, developed advancing generalised lymph node enlargement and suffered an increasingly troublesome cough. In January 1954 he was distressingly breathless and some improvement followed palliative radiotherapy. The patient died in March 1954, seven years after the diagnosis was first made and five years after the pulmonary involvement was first discovered. Permission for autopsy was refused.

Case 2. Generalised Miliary Disease

D.T., a painter aged 47, was admitted to St. George's Hospital, London, under the care of Dr. Kenneth Robson, in April 1956. Eight days before, he

* The figure numbers in the text refer to Plates III, IV, V.

had developed a pruritic rash over the trunk and limbs, followed by nausea, vomiting and diarrhœa, and on the fifth day became breathless, with a cough productive of scanty sputum. Three days before admission a carbuncle appeared on the neck. Examination showed him to be febrile (T. 100° F.), cyanosed and dyspnœic at rest. A pleomorphic rash with ulcerated patches was present on the trunk and limbs. Coarse râles and rhonchi were heard in both middle and lower aspects of the chest. The liver was enlarged, irregular and firm and the spleen was palpable. Small lymph nodes were found in both axillæ. The fundi showed many perivenous hæmorrhages.

Investigations showed white cells 11,400 per cu. mm. with a polymorphonuclear leucocytosis, blood urea 32 mg. per cent., fasting blood sugar 152 mg. per cent., and the presence of a high diffuse gamma-globulin fraction in the plasma proteins. Sputum culture produced no pathogens. The sternal marrow contained an excess of plasma cells, but biopsy of skin, liver and lymph gland showed no specific changes. The chest X-ray showed a coarse, disseminated miliary pattern throughout both lung fields with coalescence in both mid-zones and the right lower zone.

The carbuncle healed with penicillin but the condition remained otherwise unchanged. After three weeks, treatment with cortisone was started with a dose of 200 mg. daily. The liver and spleen decreased in size, the fever fell and the chest X-ray shadows diminished. On reducing the dose to 100 mg. daily, however, the shadows again became more prominent (Fig. 2) and the patient was discharged on 75 mg. twice daily. At this time the fasting blood sugar had risen to 253 mg. per cent., and impaired glucose tolerance was demonstrated.

In August 1956 the patient was readmitted with increasing breathlessness, recurrence of the rash and rectal bleeding. There was an increase in the size of the lymph nodes of the axillæ, neck and groins. The liver appeared to be about the same size as before, but the spleen had again enlarged and the pulmonary shadows had increased in the mid-zones. The glucose tolerance was further impaired and the blood count showed eosinophilia. The plasma proteins were 8·1 g. per cent. of which the globulin formed 6·9 g. per cent. Axillary lymph node biopsy showed a typical cellular pattern of Hodgkin's disease. Treatment with an increased dose of cortisone, together with insulin, was followed by a course of mustine to a total dose of 21 mg. The liver, spleen and lymph nodes decreased in size and the chest shadows showed some clearing. Shortly after, his condition again deteriorated with marked dyspnœa, and a month later the patient died. The pulmonary condition had been present from the onset of the disease six and a half months previously.

Autopsy showed two types of appearance in the lungs: some non-aerated areas were homogeneously infiltrated with hard, solid grey tissue in which prominent grey interlobular septa were present. These areas occupied much of the upper and right middle lobes. Secondly, in all lobes, but especially the lower, there was studding with numerous minute, poorly defined miliary nodules. The bronchi contained moderate quantities of muco-pus.

Case 3. Nodular Lesions with Coalescence: Miliary Tuberculosis

R.B., aged 15 years, who was admitted under the care of one of us (P.E.), first complained of an unproductive cough in March 1946, but at that time was otherwise symptom-free. The past and family histories were non-contributory. Physical examination showed only bilateral cervical lymphadenopathy, but the

chest radiograph revealed a well-defined upper mediastinal opacity (Fig. 3A), and clear lung fields. Biopsy of a cervical lymph node showed the normal architecture of the gland to be replaced by lymphadenomatous tissue with some fibrosis and slight necrosis. A blood count showed hæmoglobin 84 per cent., white cells 24,400 per cu. mm. with polymorphonuclear leucocytosis, and the E.S.R. (Wintrobe) was 42 mm. in the first hour. The Mantoux reaction was weakly positive with 1 : 1000 O.T.

Radiotherapy was given to a total dose of 1600 r with complete regression of the cervical and mediastinal lesions (Fig. 3B), but further treatment was required in October 1946 for nodes in the left iliac fossa, in January 1948 for the mediastinal mass which had reappeared, in March and September 1948 for recurrent cervical lymphadenopathy, in January 1949 for para-aortic nodes, and in November 1949, November 1950 and April 1951 for peripheral lymphadenopathy.

Although the patient's general condition had not deteriorated, in April 1951 a chest X-ray showed discrete nodular opacities of 1 to 3 cm. diameter in both lower and middle zones bilaterally, with coalescence in the right lower zone to give a confluent shadow with a poorly defined border (Fig. 3C). These regressed considerably following radiotherapy in June 1951, but in the next month he again needed treatment for an osseous deposit in the proximal third of the left femur.

In December 1951 coarse miliary shadowing was widespread in both middle and lower zones of the chest radiograph and rapidly became denser in the course of one month, but there was no recurrence of the nodular shadows. Prolonged radiotherapy failed to influence the progress of the disease. Increasing dyspnœa occurred over the next six months and, despite two courses of intravenous mustine, the patient died in August 1952, seventy-seven months from the diagnosis of Hodgkin's disease and seventeen months after the discovery of pulmonary involvement.

Autopsy by Dr. Woodhouse Price showed bilateral pleural effusions and solid, voluminous lungs with numerous firm, pale, lenticular nodules especially concentrated near the hilar regions. Histology of the lung showed miliary tuberculosis with some confluent caseation, general fibrosis of the pulmonary parenchyma, œdema, emphysema and areas of focal suppuration. Fibrinous pleurisy was present. The spleen and liver were affected by miliary tuberculosis and caseous tuberculosis was found in lymph glands. No evidence of active Hodgkin's disease was found.

Case 4. Large Nodular Lesions

A.J.W., a biochemist, was first admitted at the age of 21 to the Hammersmith Hospital under Dr. Aitken in October 1937, complaining of generalised pruritus of six weeks' duration, followed by the appearance of enlarged, tender, discrete supra-clavicular nodes in the left side of the neck. A blood count was normal, but chest X-ray showed enlargement of left anterior mediastinal lymph nodes. She had previously been healthy and there was no significant family history. Gland biopsy was reported as showing Hodgkin's disease, and the lymphadenopathy regressed following radiotherapy. In the following years she remained well, but required repeated courses of radiotherapy for affected lymph nodes in the neck, mediastinum and axillæ. Treatment was given in December 1938 to nodes in the right axilla and in 1939 to nodes in the neck. In the same

year a therapeutic abortion was performed, in the current belief that pregnancy had a deleterious effect on the condition, and in 1940 surgical sterilisation was effected.

Between 1941 and 1943 further irradiation was given to the neck and upper chest at another centre. In February 1942 she required treatment to the right axilla and to the left side of the neck, and this was repeated in 1945. Between 1946 and 1949 she was living abroad and remained well, and on admission under Professor McMichael in June 1949 the only abnormality was enlargement of two nodes in the right supra-clavicular region. These were excised and the biopsy report stated that the larger was almost completely replaced by fibrous tissue, with a few remaining islets of lymphocytic and reticulum cells. Plasma cells and eosinophils were prominent and Sternberg-Reed cells present. The smaller node retained some of its architecture, but there were areas containing reticulum cells, giant cells and plasma cells.

By January 1953 she had developed further lymphadenopathy in the right side of the neck and behind the inner third of the clavicle, with obstruction to the venous return from the right upper limb. Radiotherapy provided good relief. Chest X-ray at this time showed no mediastinal involvement. One year later she again went abroad, but from May 1954 she experienced fatigue, lassitude and general pruritus, and in June developed pain in the chest on taking alcohol.

On readmission in August 1954 she appeared generally well and was not anæmic. The right clavicle was smoothly enlarged along its whole extent and irradiation changes were present over the right axilla. A smooth, tender, poorly defined swelling was present in the soft tissue of the right upper chest, with deep attachments. Lymph nodes were palpable in the right axilla and neck, but the liver and spleen were not palpable. The hæmoglobin was normal, but an eosinophilia of 10 per cent. of 6,000 white cells was present on one occasion and the E.S.R. (Westergren) was 36 mm. in 1 hour. Chest radiography showed a large right paratracheal mass extending forward into the retrosternal space, and in the left mid-zone was a fairly well-defined, rounded opacity about 4 cm. in diameter. Other smaller opacities were present in the right middle and both lower zones. Radiotherapy reduced the soft tissue mass but did not affect the pulmonary appearances. These, however, showed moderate improvement with two doses of 7·5 mg. of mustine, and this was still maintained one year later. In February 1956 the parenchymatous lung lesions had again extended and on this occasion did not respond to chemotherapy (Fig. 4A).

By October 1956 the lung lesions had increased in size but not in number. She was again complaining of pruritus and had become increasingly breathless over the course of the previous five months. This improved while she was being treated with mustine, but several attacks clinically indistinguishable from asthma occurred. The radiographic appearances showed no marked change. In January 1957 her symptoms were again worsening and a course of chlorambucil made a transient improvement in her condition. The chest radiograph of April 1957 is shown in Fig. 4B. Her final admission was in June 1957, by which time she was losing weight and was feverish. Widespread lymphadenopathy, splenomegaly and palpable nodules in the ribs were found. The pulmonary shadows had extended to become confluent in both middle and lower zones and areas of mottled shadowing and infiltration extended superiorly.

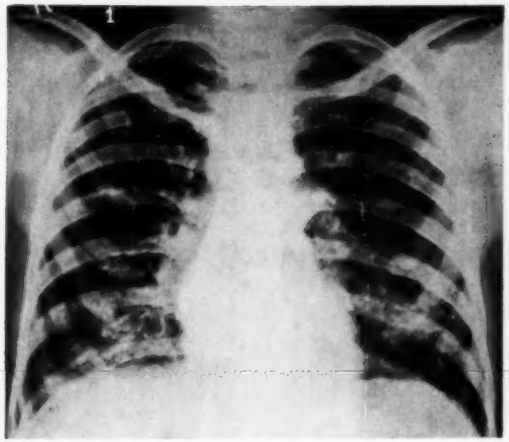

FIG. 1.—Chest radiograph of patient D.E., Case 1, showing generalised pulmonary reticulation.

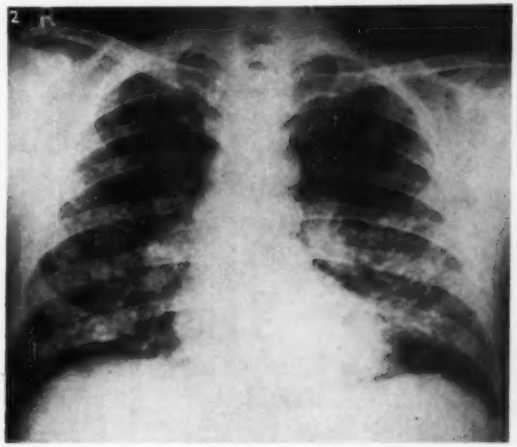

FIG. 2.—Chest radiograph of patient D.T., Case 2, showing generalised miliary shadowing of the lung fields.

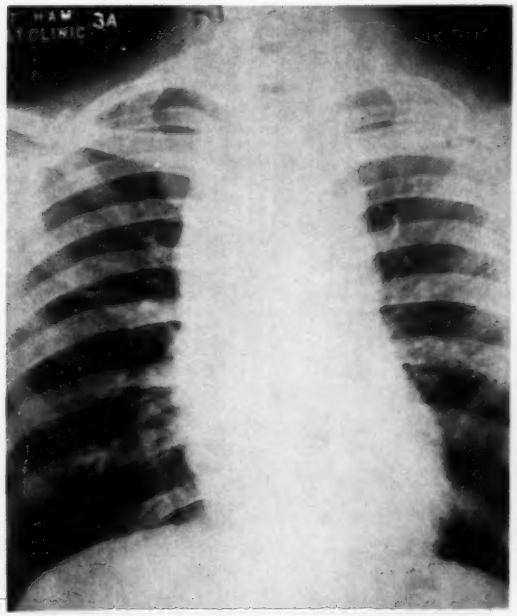

FIG. 3A.—Patient R.B., Case 3. X-ray of the chest showing a well-defined upper mediastinal opacity due to Hodgkin's disease.

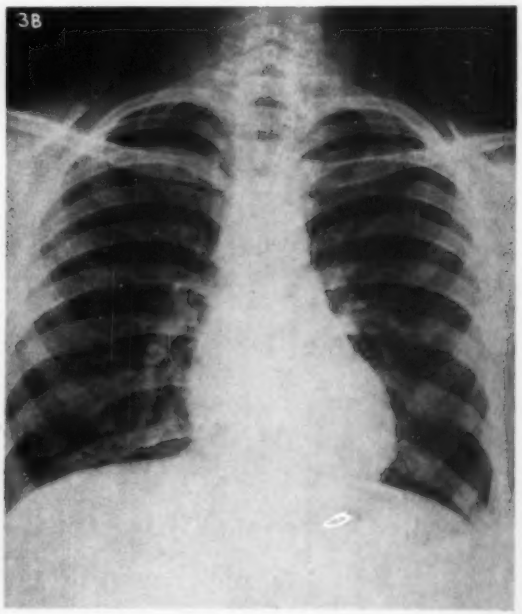

FIG. 3B.—Same case, following radiotherapy showing the complete regression of the mediastinal shadow.

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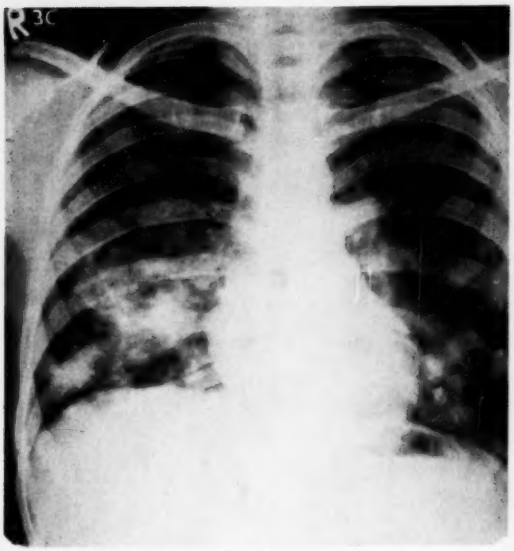

FIG. 3C.—Chest radiograph of same case showing bilateral nodular opacities with coalescence in the right lower zone.

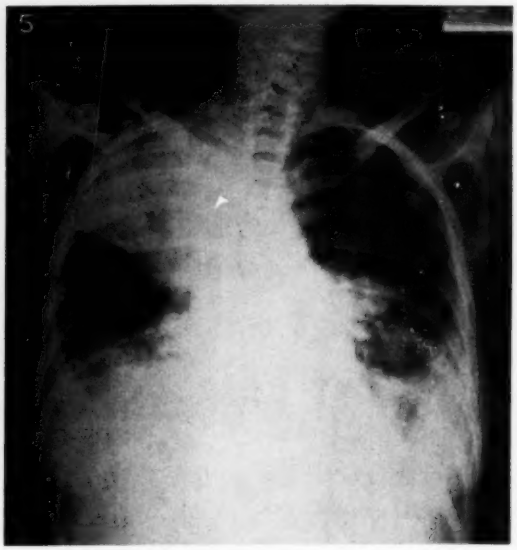

FIG. 5.—Chest radiograph of patient E.P., Case 5, during her terminal illness, to show massive lobar infiltration, cavitation, hilar infiltration, basal nodules and effusions.

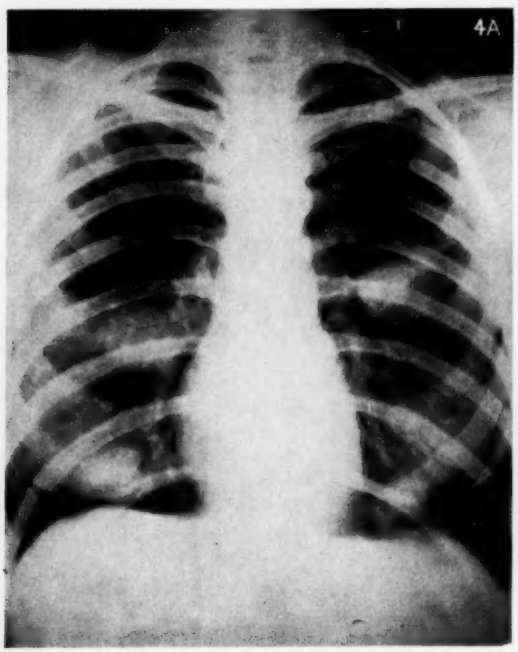

FIG. 4A.—Chest radiograph of patient A. J.W., Case 4, showing bilateral nodular opacities nineteen months after their first appearance.

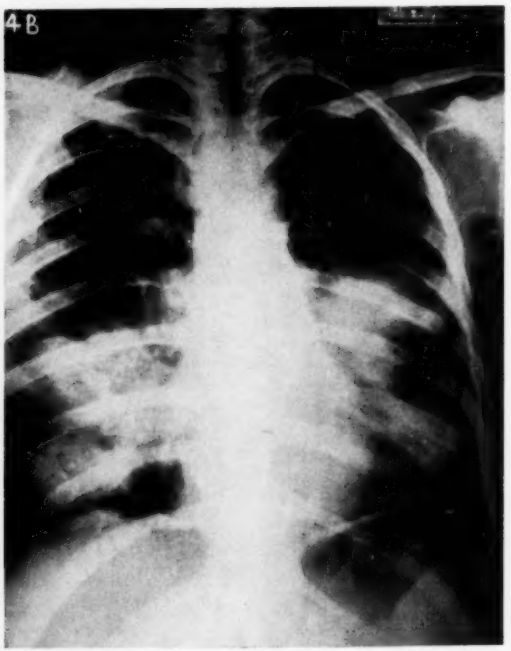

FIG. 4B.—Chest radiograph showing expansion and confluence of pulmonary nodules in patient A. J.W., Case 4, thirty-three months from first appearance.

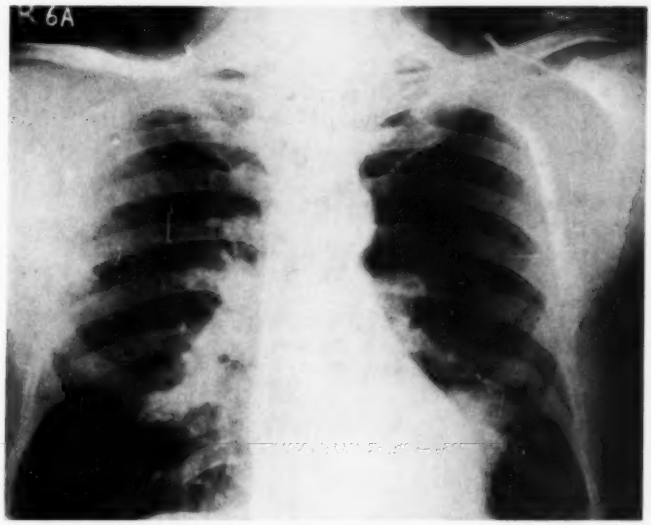

FIG. 6A.—Chest radiograph of patient F.B., Case 6, showing a well-defined lesion in the left lower lobe and an indistinct shadow in the right mid-zone.

FIG. 6B.—Chest radiograph in left lateral position, Case 6, further demonstrating the lesion in the posterior basal segment of the left lower lobe, seen in Fig. 6A.

Clinical examination showed impaired percussion and vocal fremitus with diminished breath sounds at the right base and scattered fine râles. Increasing dyspnœa led to death on June 30, 1957, nearly twenty years after Hodgkin's disease was first diagnosed, and three years from the onset of pulmonary involvement.

Autopsy by Dr. C. V. Harrison showed extensive lymph node involvement, that in the right axilla being frankly invasive, with extension into the pectoral muscles. The spleen was four times enlarged and showed typical deposits, which were also found in the right adrenal, the thyroid and the cervix uteri. Numerous deposits of tumour were in both lungs, some obstructing the bronchi and associated with endogenous lipoid pneumonia. Terminal œdema was also present, and a little free fluid in each pleural space. Bone marrow scarring was seen.

Despite the invasiveness of the condition in its later stages, the deposits seen at autopsy showed essentially the same structure as the original specimen biopsied, with extensive fibrosis and scattered reticulum cells, giant cells and eosinophils.

Case 5. *Nodular Lesions. Hilar Invasive Infiltration. Lobar Consolidation*

E.P., a housewife aged 22 years, was referred to one of us (P.E.) complaining of dyspnœa and cough in May 1953, and bilateral cervical and axillary lymphadenopathy were discovered. Biopsy of a cervical lymph node showed "a very acellular reticulo-endothelial tissue of the nature of a Hodgkin's sarcoma," and chest radiography demonstrated a large anterior mediastinal mass. In October 1953 she was admitted for treatment with mustine to a total dose of 60 mg. with great improvement. She remained well until four months later, when the mediastinal mass enlarged and the spleen became palpable, and she was troubled by generalised pruritus. Deep X-ray to the axillæ, neck and mediastinum produced a further marked improvement.

A chest X-ray in December 1954 showed no pulmonary involvement, but three months later, when she was complaining of malaise, abdominal discomfort and loss of weight, the chest X-ray revealed rounded homogeneous opacities about 2 cm. in diameter in the right middle zone and both lower zones, with some confluence on the left. There was no evidence of the mediastinal mass. At this time there was a recurrence of the nodal enlargements in the neck and axillæ, and hepato-splenomegaly. Investigations showed hæmoglobin 76 per cent., a normal white cell count, E.S.R. (Westergren) 60 mm. in one hour, and no A.F.B. demonstrable in the sputum. A course of tri-ethylene melamine was given to a total dose of 75 mg. in five weeks. The response was good, with improvement in appetite and weight and reduction in the lymphadenopathy. There was virtual resolution of the pulmonary lesions.

In September 1955 there was evidence of a recurrence of the pulmonary deposits. A transient episode of jaundice subsided spontaneously but reappeared shortly after, and inguinal lymphadenopathy was detected. Radiotherapy to the abdomen and groins was followed by resolution of both the jaundice and the enlarged glands, but within six months she had again developed generalised lymphadenopathy and was becoming anæmic. Radiotherapy led to a short-lived improvement, and by August 1956 she was paler, anorexic and had a troublesome cough and dyspnœa. In January 1957 she had reached a terminal state, with anæmia, wasting, pruritus, generalised lymphadenopathy and severe

dyspnœa requiring continuous oxygen. The chest radiograph showed consolidation of the right upper lobe with cavitation, hilar infiltration and pulmonary deposits in the lower zones (Fig. 5). Bilateral pleural effusions were also present.

Despite further irradiation the patient died forty-four months from the first signs of the disease, and twenty-two months from the first recognition of pulmonary involvement. Autopsy could not be obtained.

Case 6. *Hodgkin's Disease restricted to the Lung*

F.B., an engineer aged 50, had a mass miniature X-ray in May 1958 which demonstrated a shadow in the left lower lobe. He had no symptoms and no serious illness in the past. A previous M.M.R. in 1955 had been normal. Full plate chest radiography showed a rounded shadow in the left lower lobe, and a small indefinite lesion in the right middle zone. Bronchoscopy demonstrated no abnormality. A tentative diagnosis of bronchial carcinoma was made and the patient was referred to Mr. Meredith Brown, and was admitted for further investigation to the Milford Chest Hospital. The chest X-rays (Figs. 6A and 6B) in September 1958 showed the left-sided lesion to have enlarged, and right lateral tomography showed partial collapse of the right middle lobe and a small round shadow in the posterior segment of the upper lobe.

On October 2, 1958, a diagnostic left thoracotomy was performed and a solid lesion about the size of a small orange was found in the sub-apical region of the left lower lobe. It was fairly hard, somewhat nodular and greyish-yellow in colour. The diseased area extended beneath the surface of the lung towards the anterior basal segment and separate small nodules were seen more anteriorly, these being 1 or 2 mm. in diameter. The adjacent lung tissue was a little inflamed, but there was no suppuration. The interlobar fissure was complete, but the disease extended to a small extent across an adherent area into the upper lobe, which was normal apart from a small apical scar. Specimens were taken for biopsy from the centre of the lesion and from the superficial extension. No enlarged or abnormal lymph nodes were found in the chest.

The sections were sent to Dr. Hinson, who reported them as showing Hodgkin's disease. The patient remained symptom-free, but by December 1958 the lesions were again enlarging and radiotherapy was advised. He remains under observation.

Discussion

The most striking feature of pulmonary involvement in Hodgkin's disease is its remarkable diversity, and Held (quoted by Versé, 1931) has said that " the picture is typical by reason of its protean features." An individual case may show more than one type of lesion (Fein and Meeker, 1937), and this is illustrated by Case 5 in which nodular, infiltrative and lobar lesions were all present terminally. There is moreover no definite evidence to suggest that the various types bear any constant relationship with prognosis, response to therapy, or symptomatology, and as with so many features in such a variable condition as Hodgkin's disease, their significance can only be assessed within wide limits.

The patterns assumed by the lesions depend to a considerable degree on their mode of spread within the lung. Probably the commonest means is by

direct extension from a mediastinal mass (Yardumian and Myers, 1950) to give invasive lesions most prominent at first about the hilar regions. The bronchi may be conspicuously involved, with extension along these and in the peribronchial tissues, and later spread to the adjacent alveoli. Scheinmel *et al.* (1950) regard nodular densities arising along the bronchial tracts as originating in this manner. The lymphatics also provide a pathway for retrograde spread, which may account for the reticular patterns seen radiographically. Simonds (1926) describes " white radiating bands " following the course of the interlobular lymphatics. Despite the absence of evidence for blood-borne metastasis between organs in Hodgkin's disease, certain lesions within the lung appear to arise in this manner (Gibbons, 1906; Stewart, 1926; Hartfall, 1932; Weber, 1930), and this may determine the distribution of multiple localised and generalised lesions. On gaining access to the parenchyma further extension of the disease process may proceed by replacement of lung tissue by growth (Schottelius, 1906; Chiari, 1911) or by granulomatous invasion of the alveoli (MacCallum, 1907). Moolten (1934) has described an " exudative phase " in alveoli ahead of the advancing edge of Hodgkin's tissue, with fibrin deposition followed by granulomatous replacement or organisation by fibroblasts. Interstitial infiltration may also be prominent and has been emphasised by Holesh (1955). The massive lesions involving a lobe or more are not simply explained, but are probably due to direct spread through the lobe, perhaps preceded by some degree of collapse associated with an endobronchial lesion or hilar gland involvement. In other cases it appears to result from the fusion of multiple smaller lesions.

From a clinical aspect, pulmonary lesions in the presence of Hodgkin's disease may be divided into the following groups:

(1) true parenchymal pulmonary involvement with Hodgkin's disease evident elsewhere,
(2) pulmonary Hodgkin's disease " in isolation," without extra-pulmonary features,
(3) pulmonary complications of mediastinal or bronchial disease without invasion of the lung, and
(4) incidental pulmonary disease in a patient with Hodgkin's lymphoma.

As has been seen, a wide variety of true parenchymal lesions occurs, and these are summarised in the classification in Table I. Briefly, the radiographic appearances of the localised lesions may suggest nodules, varying in size, number, definition and distribution (as in Cases 3, 4 and 5), which may show coalescence into extensive masses (as in Case 4), or there may be massive lobar involvement (as in Case 5), or confluent lesions involving more than one lobe and in continuity with the mediastinal nodes (Fein and Meeker, 1937). Peribronchial spread may result in feathery shadows or streaking in the lung fields, while irregular, often poorly defined, hilar shadows result from local invasion. The diffuse shadows may be reticular, as in Case 1, and these seem to appear earlier in the course of the disease and to be of more benign significance than other pulmonary shadows in this condition. Miliary and " lymphangitic "

types of diffuse involvement also occur, and may be virtually indistinguishable from miliary tuberculosis, sarcoidosis, and lymphangitis carcinomatosa (Holesh, 1955).

Case 6 provides an excellent example of pulmonary Hodgkin's disease " in isolation," since no mediastinal lesion was demonstrable in the standard chest X-ray, in right lateral tomograms or on left-sided thoracotomy, and there can be no reasonable doubt that it took origin from pulmonary lymphoid tissue. The occurrence of lymphomatous change in autochthonous foci in the lung had been suggested for many years (Wessler and Greene, 1920) as an explanation of certain nodular lesions, but lacks definitive proof. Lesions isolated to the lungs have at various times been described as " primary Hodgkin's disease of the lung " (for example, Weber, 1930; Versé, 1931; Yardumian and Myers, 1950), but cases in which the term has been applied have not invariably shown disease confined to the lung parenchyma.

Thus, the case described by Charr and Wascolonis (1941) showed, in addition to a large mass in the right middle and lower lobes, affected glands in the neck and mediastinum, and the possibility of the disease having arisen here is not easily refuted. Terplan (1922) has emphasised the rarity of the primary lung lesion, and it is not easy to prove the absence of disease elsewhere before autopsy, since possible preceding sites in lymph nodes or spleen may remain clinically undemonstrated. It therefore seems preferable to refer to pulmonary sites " in isolation " where extra-pulmonary disease is not encountered, rather than be committed to a diagnosis of " primary " disease which must of necessity be less than proven during life, and carries the implication of describing the initial site of the disease. Although pulmonary disease is rare in the absence of mediastinal involvement, the extension of a lesion established in the lung is not necessarily dependent on, or correlated with, the continued enlargement of the mediastinal mass from which it takes origin, as can be seen in Cases 4 and 5, in which the pulmonary lesions continued to spread, despite the comparative quiescence of the mediastinal disease following treatment.

One terminal feature of Case 5 was the presence of cavitation in a massive lobar infiltrate. The relative frequency of this is disputed, but cases have been described by Versé (1931), Bouslog and Wasson (1932), Efskind and Wexels (1952), and Dickson and Smitham (1952). Such cavities may vary from small multiple necroses in nodular lesions to massive spaces as described by Weber (1930), and in general they must be regarded as an indication of a worsening prognosis. Craver (1941) felt that they were usually due to some secondary factor such as bronchial occlusion with infection, or tracheo-œsophageal fistula, but they can also occur spontaneously.

Pulmonary lesions secondary to mediastinal or bronchial disease include atelectasis, massive collapse or lung abscess, and recurrent infections may follow secondary bronchiectasis. Partial collapse is uncommon, and Moolten (1934) associated this with the poor expansile tendency which he found in the intrapulmonary lesions. Massive collapse is rare, and is usually ascribed to bronchial occlusion due to pressure from enlarged lymph nodes (Rubin, 1947). However, in the case described by Hardin (1939) the main factors were the

tenacious mucopurulent sputum and chronic endobronchitis, and collapse of multiple lobes resulting from endobronchial deposits has been described (Vaughan, 1958). One further and often confusing event is the development of post-irradiation fibrosis, and this may be indistinguishable radiographically from a true parenchymal Hodgkin's infiltration.

Of the incidental pulmonary diseases complicating Hodgkin's disease, probably most attention has been directed to tuberculosis, which was a prominent feature of the terminal period of Case 3. It has long been felt that there is an especially close relationship between the two conditions, and at intervals the view has been expressed that Hodgkin's disease is a variant of tuberculosis. The various aspects of this controversy have been extensively reviewed by Hoster and Dratman (1948), and a most convincing comment has been made by Horder (1932), who said, concerning the frequency of the association of the two diseases: ". . . when it is remembered that lymphadenoma is a common disease and lowers the vitality very considerably, the incidence scarcely calls for special comment, still less provides a reasonable confirmation of the hypothesis that Hodgkin's disease is itself an expression of tuberculosis." In addition, it may be that quiescent tuberculous lesions are activated by irradiation (Jackson and Parker, 1944) or by invasion from Hodgkin lesions, and that disturbance of the immune processes in Hodgkin's disease is also important.

To distinguish associated tuberculosis from parenchymal disease in a patient already known to be affected by Hodgkin's disease may be difficult, though Holesh (1955) points out that in the presence of cavitation an irregular, craggy wall is in favour of lymphadenoma. In view of the anergy to tuberculin shown by patients with Hodgkin's disease (Parker *et al.*, 1932) a strongly positive Mantoux reaction may be very significant.

With regard to the clinical effects of pulmonary Hodgkin's disease, it is difficult to ascribe symptoms to the condition specifically, since cough, sputum and dyspnœa, together with anorexia, weight loss, fever, weakness and pruritus, may all occur while the disease is still confined to the mediastinum. It is evident, however, that pulmonary lesions may contribute to the severity of these, since they may worsen during the extension of pulmonary deposits, despite persisting quiescence of the disease in the lymph nodes. One notable feature is the infrequency of hæmoptysis in the condition, but this occurred in one case described by Moolten (1934), due to a polypoid bronchial growth, and in the cases of Hardin (1939) and Charr and Wascolonis (1941), in which endobronchial infiltrations were found. With regard to the effect of pulmonary involvement on the survival of the patient, Scheinmel *et al.* (1950) felt that death was due to predominantly lung disease in only 11 of 35 affected cases; despite this, the advent of the involvement of the lungs often indicates a poor prognosis (Jackson and Parker, 1946), since it tends to occur in advanced cases (Van Hazel and Jensik, 1956). The study made by Levinson *et al.* (1957) indicated that it was a more sinister event than mild anæmia, mediastinal involvement or pruritus, but less sinister than involvement of skin, bone, liver or spleen. Their statistics suggested that lung involvement was a feature of the last quarter of

the period of survival, but the variability of the condition is such that this is of only limited value in assessing the individual case.

It can therefore be seen that a wide spectrum of pulmonary expression may be present in Hodgkin's disease, and it may well be that these manifestations will become more prominent, if not more common, as advances in therapy improve the prospects of survival in this disease. If so, problems arising in their recognition and management will require increasing attention, since it occurs so often in Hodgkin's disease that the well-being of the patient depends on careful appraisal of secondary and sometimes apparently marginal features of his condition.

Summary

Six cases of Hodgkin's disease are described, illustrating different aspects of pulmonary involvement; two showed generalised forms, three had essentially localised lesions, and in one case the pulmonary features were the only manifestation of the condition when the case presented.

The variability of the disease is emphasised, and its nature, course and significance are discussed.

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"THE COUGHING DISEASE" IN CHILDREN

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This country has long been noted for its high incidence of respiratory disease. For this our climate is frequently blamed: even the Romans referred to our island as the land of fogs. Reid (1958a) points out that the sudden climate changes at the approach of winter precipitate minor respiratory infections which are the forerunners of much more serious respiratory illnesses. In Harrow bronchitis is the fifth commonest cause of death. Table I shows the number of new cases of respiratory tuberculosis and of chronic bronchitis seen over recent years, together with the number of deaths due to these two causes occurring in the borough of 219,000 people.

Table I.—Showing the Number of New Cases of Respiratory Tuberculosis and Chronic Bronchitis seen at the Chest Clinic, and the Number of Deaths in the Area

	Respiratory tuberculosis		*Chronic bronchitis*	
	New cases	*Deaths*	*New cases*	*Deaths*
1949 ..	262	55	—	117
1955 ..	160	13	230	100
1956 ..	148	13	271	106
1957 ..	124	12	276	80
1958 ..	107	8	353	107

The definition of chronic bronchitis is difficult and the term is, in practice, a popular label for the symptoms cough, sputum and dyspnœa. It is probably better to think in terms of a coughing disease, since coughing is the main trouble. For the established syndrome treatment is disappointing and is mainly palliative so that more attention is being directed to the preventive aspect. Oswald *et al.* (1953) in tracing the natural history of chronic bronchitis found, from the answers to a questionnaire, that chronic or recurring respiratory infections had been commoner in those who later developed chronic bronchitis than in a control group. Their periods of absence from school had been longer and absences of even an occasional week were more frequent. Reid and Fairbairn (1958) also found, in reviewing the histories of Post Office workers with chronic bronchitis, that in early adult life those destined to become disabled by chronic bronchitis had more and longer absences from work owing to bronchitis than their fellows of the same age. They found the same general trend equally apparent in the frequency of absence due to colds and other upper respiratory tract infections.

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It seems possible from these retrospective investigations that a disposition to respiratory illness may go back to early childhood. This supposition, combined with the poor results obtained in the treatment of chronic bronchitis, has stressed the importance of the development of a children's clinic for respiratory disorders. In the years 1955-57 out of a child population of 47,400 the Harrow general medical practitioners referred 2,442 cases for a chest X-ray and tuberculin test, distributed as follows:

		Per cent.
0- 4 years	419	(17)
5- 9 ,, ...	1,117	(46)
10-14 ,, ...	906	(37)

That the majority of these had a cough as one of their symptoms shows how common this is in childhood. In many there had been an acute respiratory illness of short duration and the chest X-ray was considered to be normal. In 675 further investigation was required because of a radiological abnormality or because of the prolonged duration of symptoms. These fell into the following groups:

		Per cent.
Non-respiratory illness ..	152	(22)
Tuberculosis (respiratory and non-respiratory)	89	(13)
Single acute respiratory infection of short duration (*circa* two weeks	69	(10)
Upper respiratory tract infection of prolonged duration	213	(32)
Recurrent bronchitis ..	100	(15)
Allergic asthma	42	(6)
Bronchiectasis	10	(2)

The greatest number of cases was due to upper respiratory tract infection, of which 35·6 per cent. had radiological evidence of areas of aspiration pneumonitis. The broncho-pulmonary segmental distribution was as follows:

	Per cent.
Unilateral basal segments	31
Bilateral basal segments	27
Middle lobe	18
Lingula	8
Unilateral upper lobe segments ..	16

Under the heading of recurrent bronchitis has been included those cases characterised by sputum retention. These cases frequently follow attacks of pertussis. They have a recurrent cough with periodic vomiting, which seems to be an attempt to clear their chests, and the X-ray shows areas of collapse and consolidation at both bases. All cases of recurrent bronchospasm which were believed to be predominantly infective in origin have also been included. Allergic asthma was only accepted after prolonged observation, and as a result of this policy a minimum number was diagnosed. Bronchiectasis is also probably more frequent than shown, since bronchograms were only performed in those cases in which suggestive symptoms persisted, and these usually only when the child was approaching the age when operation had to be considered.

In spite of this policy the incidence represents 4·1 proven cases per thousand children X-rayed.

The age distribution of these different groups of children is shown in Fig. 1. There is a big incidence of cases of upper respiratory tract infection, recurrent bronchitis, single acute respiratory infection and tuberculosis at the ages of 5

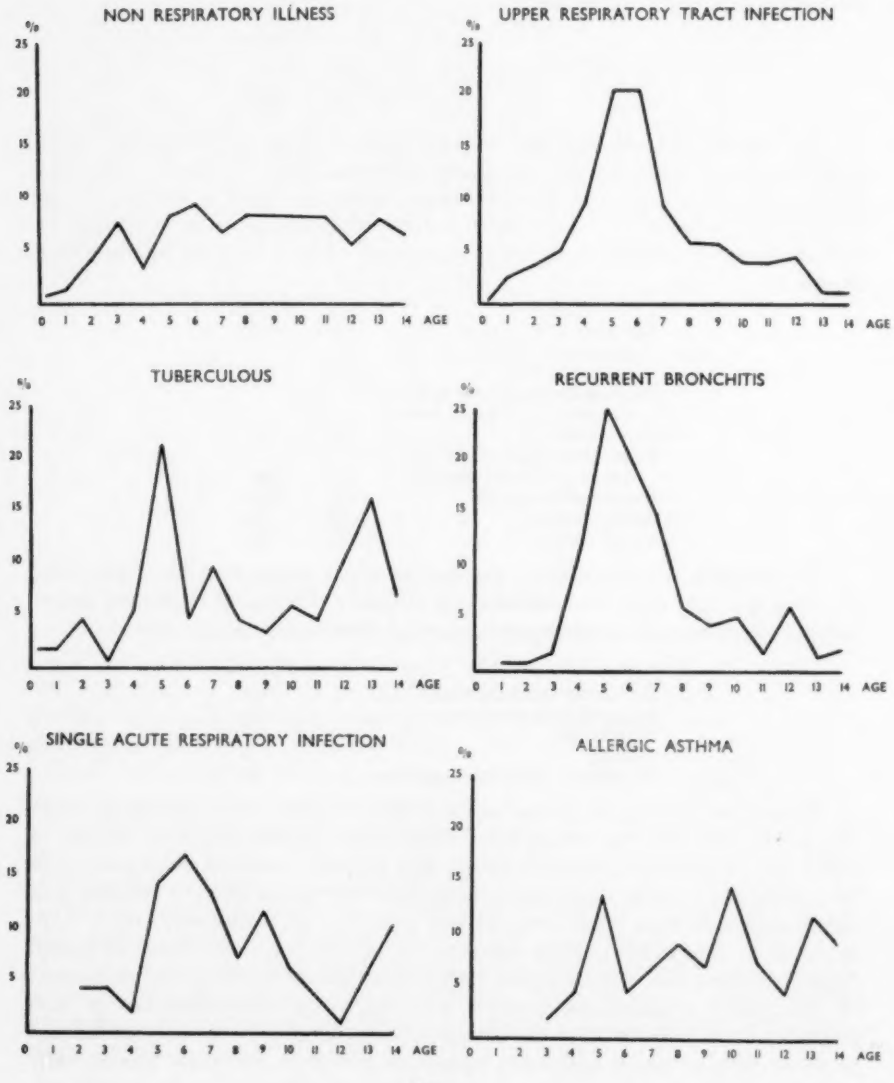

FIG. 1

and 6. This is probably related to starting school and the spread of infection amongst children by direct contact through the poor personal hygiene usual at this age. This is supported by the percentage in each group who were " only " children and presumably acquired their infections at school and not at home (Table II). There was more than double the percentage of " only " children with recurrent bronchitis than those with non-respiratory illnesses. In the case of non-respiratory illnesses and allergic asthma there was no rise in incidence on starting school, the cases being distributed through all childhood.

Treatment of respiratory infections has been on relatively simple lines. Antibiotics have only been used where symptoms were severe with much constitutional upset. The cough arising from upper respiratory tract infection, aspiration pneumonitis, and sputum retention, is easily controlled by raising the foot of the bed at night by the placing of three bricks under each bed foot and either removing the pillow or replacing it by a shallow one. Children seem

TABLE II.—SHOWING THE NUMBER IN EACH GROUP WHO WERE " ONLY " CHILDREN

	Number seen	*Number " only " children*	
		Per cent	
Non-respiratory illness	152	35	(23)
Tuberculosis (respiratory and non-respiratory)	89	36	(40)
Single acute respiratory infection of short duration (*circa* two weeks)	69	23	(33)
Upper respiratory tract infection of prolonged duration ..	213	54	(25)
Recurrent bronchitis	100	28	(28)
Allergic asthma	42	7	(17)
Bronchiectasis	10	2	(20)

unable to raise sputum and this measure has quickly cleared shadows at the bases of the lungs. Further trickling down of secretions from the nose into the lungs with the possibility of further pulmonary damage is also prevented by this measure. As a result the child usually sleeps well after a few days, with a resulting improvement in liveliness and appetite. The gratitude of the mothers whose sleep is no longer disturbed is great. A nasal spray of antistin-privine or neo-endrine for a short period has also been used. The main emphasis has thus been on the prevention of pulmonary damage, since it has been found that by the age of 7 the number continuing to suffer from nasal catarrh is low. After this age catarrh has often meant that sinus infection has been present, requiring intervention.

Recurrent bronchitis and bronchospasm have usually responded to breathing exercises originally taught by physiotherapists and then supervised by the mother at home, so that the natural cleansing powers of the bronchial cilia could have full play. The same régime has been applied to cases of allergic asthma, and allergy tests and desensitising injections have only been used after trial of these other measures.

Discussion

The findings reported here show that coughing is a frequent symptom in children. There is a big increase in incidence on starting school and this catarrhal stage seems to persist until age 7, by which time immunity seems to have developed. This finding is in conflict with that of Brimblecome *et al.* (1958), who found the incidence of colds and chronic catarrh to be highest in the 0-4 age group in families having three children, one of which was under 5, living in flats and tenements in Paddington. It is in keeping, however, with the findings of Badger *et al.* (1953), Buck (1956) and Lidwell and Sommerville (1951), who worked in areas more comparable with that considered here. Direct contact has been shown to be the most important way of spread of respiratory infections (Andrewes, 1949; Buck, 1956; Lidwell and Williams, 1954; Lovelock *et al.*, 1952; and Reid, 1958b). The number of " only " children in this series points to the importance of the school in this spread.

Although the clinic developed on the theory that the appropriate treatment of respiratory infections in childhood may prevent chronic bronchitis later, the clearing of these infections by the age of 7 does not lend support to this view. It appears that chronic catarrhal infections are extremely common in childhood, and those who later develop chronic bronchitis can easily produce such a preceding history and are more likely to recall it than normal controls. Chronic catarrh is also particularly marked in young women and yet chronic bronchitis is a disease predominantly affecting men. It may be of course that, because of treatment, these children cleared up but, on the other hand, allergic manifestations were found to be spread throughout the whole of childhood, and it is possible that sufficient attention has not been paid to the allergic element in respiratory infections. Certainly different allergens seem able to produce a clinical picture indistinguishable from bronchitis.

Great emphasis has been placed on the prevention of pulmonary damage, but the incidence of this has been found to be quite high. Although it is thought that a minimal number of cases of bronchiectasis has been diagnosed these cases gave a rate of 4·1 per thousand children X-rayed. This compares with an incidence in the population of 1·3 per thousand (Wynn-Williams, 1953). More attention probably needs to be paid to the preventive aspects of coughing in children. Few mothers seem to teach their children the correct way of blowing their nose by clearing one nostril at a time, or to see that they do this frequently. The introduction of breathing and postural exercises, as taught by physiotherapists, into the physical exercise session in the infants' schools would also be a help.

Summary

An analysis of 675 children referred to a chest clinic is reported. The majority cleared with simple measures and only allergic manifestations seem to persist throughout childhood. The relation of respiratory infections in childhood to chronic bronchitis in adults is discussed.

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THE TREATMENT OF ASTHMATIC CHILDREN BY HYPNOTIC SUGGESTION

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Although hypnosis has been used in the treatment of asthma by many people, only occasional mention is made of it in the literature (Fry, 1957; Kennedy, 1947; Lloyd, 1934; Stewart, 1957). Mason and Black (1958) reported apparently striking effects obtained in an allergic subject, with both clinical improvement and alteration in skin reactions to specific allergens, as a result of hypnosis.

A blind clinical trial was planned, using hypnosis with suggestion to treat children suffering from chronic asthma and with a simple interview with the psychiatrist in the controls. The statistical method chosen was sequential analysis and assessment of results was to be made in the same way as in a previous trial reported by one of us (Smith, 1958). The controlled trial had to be abandoned because of complete failure to obtain significant objective improvement in any of the cases so that the statistical diagram remained blank. We report here only the failure to obtain any objective improvement, either immediate or delayed, by treating 25 children with hypnotic suggestion. Subjective improvement was, however, claimed by a number of them.

Material

The patients were all children of 8 to 15 years of age who had been attending the Asthma Clinic for more than six months. There were 17 boys and 8 girls. The average age was 10·9 years They had suffered from asthma in most cases for many years. The shortest duration of the condition among them was 2 years and the average age of onset of the asthma was 3½ years.

Method of Treatment

Each child was hypnotised on four occasions at weekly intervals, and during hypnosis it was strongly suggested that immediate and progressive relief from asthma would be obtained. The cases reported here were all satisfactory subjects in whom hypnosis was successful.

Method of Assessment

Any definite improvement was sought. The degree of improvement was not considered of importance, but clearly seen objective improvement of any degree would have been accepted. Respiratory function tests were made the week before treatment; before and after treatment on the days when the patients were hypnotised, and, finally, the week after treatment. Figs. 1 and 2 show the

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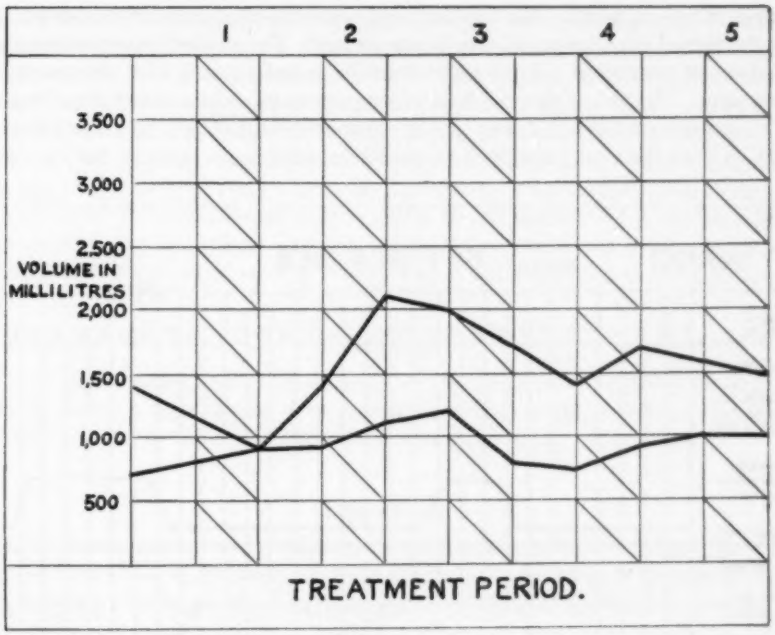
1
2
3
4
5
3,500
3,000
2,500
VOLUME IN MILLILITRES
2,000
1,500
1,000
500
TREATMENT PERIOD.

FIG. 1.

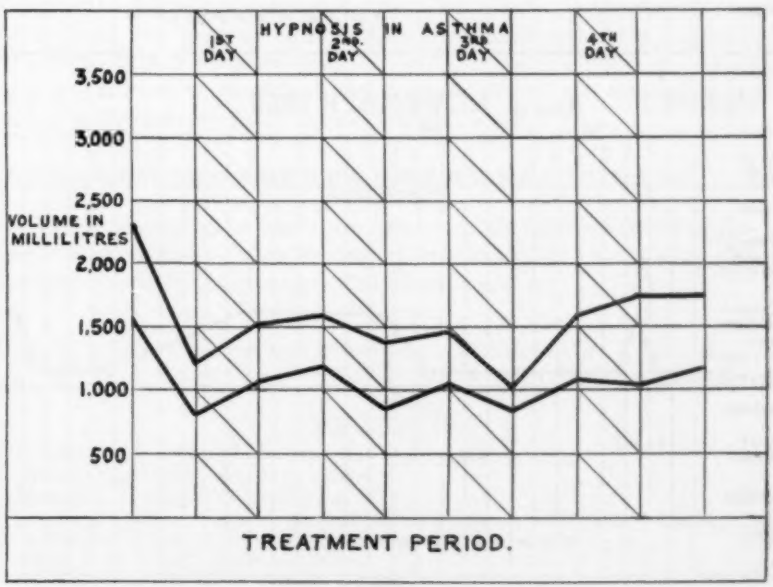
1ST DAY
HYPNOSIS
2ND. DAY
IN ASTHMA
3RD DAY
4TH DAY
3,500
3,000
2,500
VOLUME IN MILLILITRES
2,000
1.500
1.000
500
TREATMENT PERIOD.

FIG. 2.

records of two children. The top line represents the vital capacity and the lower line the forced expiratory volume in one second. The shaded columns represent the days of treatment. Tests were done both before and after treatment on these days. The use of this method of assessment in asthma has been discussed by Thompson and Hugh-Jones (1958). Improvement should be clearly seen by a rise in both the vital capacity and the forced expiratory volume, but the latter

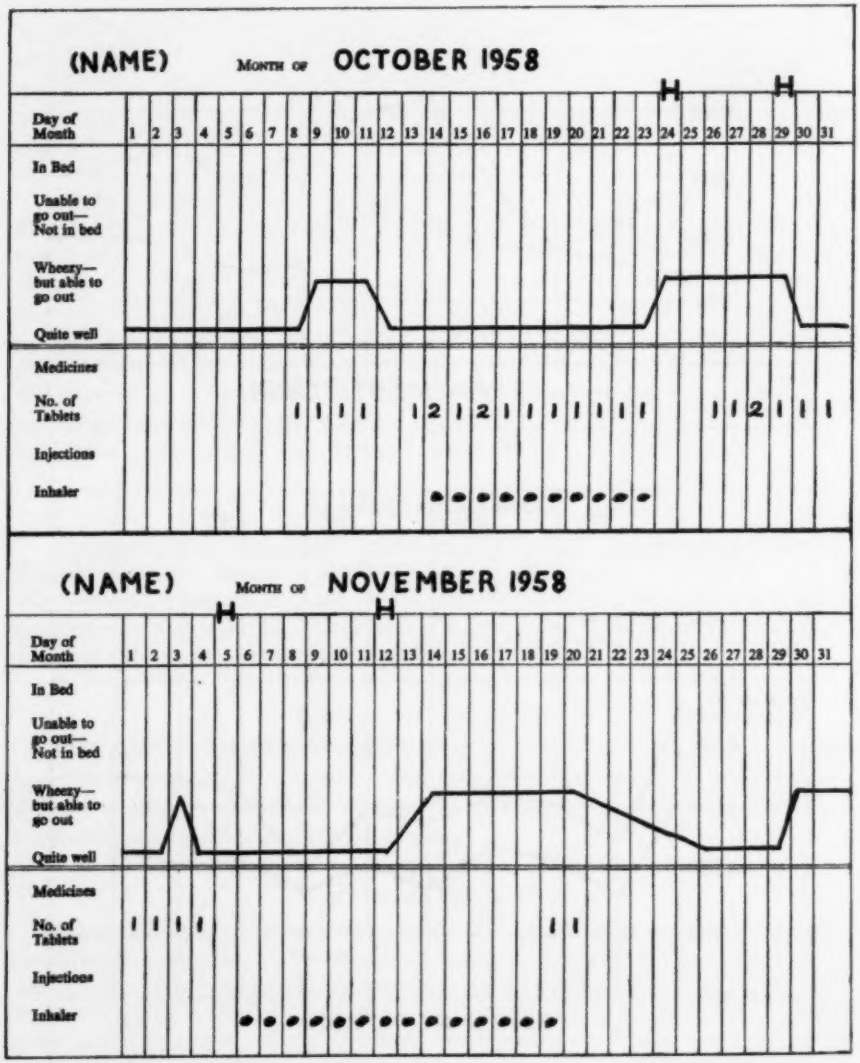
(NAME)
Month of OCTOBER 1958
H
H
Day of Month
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
In Bed
Unable to go out—Not in bed
Wheezy—but able to go out
Quite well
Medicines
No. of Tablets
Injections
Inhaler
(NAME)
Month of NOVEMBER 1958
H
H
Day of Month
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
In Bed
Unable to go out—Not in bed
Wheezy—but able to go out
Quite well
Medicines
No. of Tablets
Injections
Inhaler

FIG. 3.

should rise to a greater degree so that the gap between the lines would be narrowed. This did not occur. To supplement the respiratory function records, daily symptom record cards were kept by all the patients. These have previously been described (Smith, 1958) and are in general use in the clinic as a guide to progress. The record is kept by marking the card to indicate whether the child was completely well, wheezy but able to go to school, unable to attend school but not in bed or confined to bed. As a check on the severity of the symptoms the number of antispasmodic tablets taken or the number of times an inhaler was used is also recorded. On the whole these simple records have proved reliable over a period of several years. Fig. 3 illustrates the records obtained.

Results

As already stated, there was no evidence of improvement either immediately after hypnotic suggestion or over a period of four weeks in any of the cases. Records similar to those illustrated were obtained in the other cases.

Discussion

Objective assessment of treatment in asthma is essential. Although little has been written about it, hypnosis has been widely believed to be of value in asthma. The children proved good subjects for hypnosis and the psychiatrist confidently expected good results, having obtained apparently successful results on many occasions during thirty years of practice in psychiatry, with both adults and children. The failure to obtain good results may be due to the short duration of the treatment, but even the most superficial form of suggestion is expected to give a percentage of positive results in asthmatics which has been reported as high as 33 per cent. by Frankland and Augustin (1954) and was 14 per cent. in a trial with children similarly assessed (Smith, 1958).

Summary

Hypnotic suggestion on four occasions at weekly intervals failed to give any objective improvement, either immediate or delayed, in a series of 25 children of between 8 and 15 years of age, with chronic asthma.

We wish to express our gratitude for the help and advice of Dr. V. H. Springett and Dr. Ian Sutherland, and for the assistance of the nursing staff of the Asthma Clinic.

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TRAUMATIC CHYLOTHORAX IN A CLOSED CHEST INJURY

REPORT OF A CASE

By Desmond Rea

From Queen Mary's (Rochampton) Hospital

The first report of rupture of the thoracic duct as a closed chest injury was published by MacNab and Scarlett in 1932, and the first case to be cured by surgical intervention in traumatic chylothorax was reported by Lampson in 1948. Only 20 cases that have responded to surgical treatment have since been presented.

The following case of traumatic chylothorax that responded to surgery seemed worth reporting.

D.B., a labourer aged 28, was admitted to Mile End Hospital on February 16, 1957, following a crush injury due to numerous two-inch planks falling on to his chest.

He was distressed and dyspnœic on admission but soon recovered. He remained comfortable until four days later, when he become dyspnœic, sweaty and cyanotic. Clinical examination then showed the apex beat displaced markedly to the left and there were signs of massive pleural effusion on the right.

The X-ray on admission was normal, but four days later there was a large collection of fluid in the right lung producing an opaque right hemi-thorax radiologically but no abnormality on the left side.

Chest aspiration produced 600 c.c. blood-stained milky fluid; the milkiness was not removed by centrifuging. An analysis gave the following results:

Protein—4·7 g. per cent.; there were no organisms.
Cytology—RBC +++ and a fair number of lymphocytes.
Culture—repeatedly sterile.
Ether-soluble—substance, 2·1 g. per cent.

He then appeared to recover for several days, but on February 26 again became distressed and sweaty. Further thoracentesis yielded 16 oz. of similar fluid which continued to accumulate rapidly with corresponding aggravation of respiratory symptoms.

Subsequently, daily thoracentesis was required, producing an average of 2 pints of chyle each time.

His distress was always alleviated by thoracentesis, but he required transfusions of plasma and dextrose saline to correct the associated oligæmia.

The patient was transferred to the Middlesex Hospital on March 5, where thoracentesis delivered a further 7 pints of chyle on subsequent days. The acidosis which had also developed was treated by sodium lactate infusions prior to operation.

At an operation on March 8 (Mr. Belcher) right thoracotomy and ligation

of the thoracic duct was performed. The chest was opened through the seventh interspace on the right side. There was a moderate amount of chyle in the chest, coming from a rent in the thoracic duct as it lay on the body of the tenth or eleventh thoracic vertebra. The duct was underrun with a suture tied off and the chest was closed with a drainage tube into the pleural cavity.

The patient made an uninterrupted recovery. In addition to the electrolyte deficiency he also had a severe protein deficiency, with ankle œdema. This cleared up following a reinforced diet. He was discharged on March 27, 1957, and is now back at full work.

He was last seen in May 1959, when he confirmed that he felt completely fit.

Discussion

Lorgelat in 1663 was the first to describe the condition of chylothorax and the first authentic case was reported by Heinrich Quinke in 1875. Shackleford and Fisher reported a series of 41 cases in 1938. Two of these were their own, and they presented a summary of 39 other cases reported between 1695 to 1936, over half being due to crushing injuries of the chest and only 8 occurring in open wounds, such as bullet injuries.

Lampson in 1948 reported 18 cases of chylothorax covering the subsequent period 1936 to 1947. Eight followed closed chest injuries, and the remaining 10 cases were due to surgery or open chest wounds. Only 1 occurred in a crushing injury.

Goorvitch in 1955 reported 11 more cases of chylothorax, one of these being due to a mild blow on the chest.

Valle (1955) reported 5 cases of traumatic chylothorax in two and a half years in the Korean war. Three of these were due to crushing injuries in the chest.

Mode of Onset

An initial latent period when the patient suffers only from direct effect of his injury is characteristic. Chest X-rays taken at this stage show no effusion. The average latent period is twelve days, but may vary from one day to nine weeks; this interval is not a factor in the prognosis nor an indication of the degree of severity of the lesion.

Presentation

The presenting symptom is usually dyspnœa due to the massive effusion. If the accumulation of lymph is rapid, blood pressure falls and the pulse rises. The effusion is usually right-sided, probably because the only part of its course where the thoracic duct is in contact with the pleura is on the right side.

On paracentesis the fluid produced is a pink creamy colour (the chyle being initially blood-stained). Confirmation of its chylous nature is obtained by microscopy. The presence of fat globules and a high protein content are pathognomonic.

Ætiology

The mechanism of actual duct injury is difficult to explain. The duct may be stretched over the hyperextended spine and part of the circumference of the wall is ruptured. Cellan-Jones and Murphy (1940) report a post-mortem on a case in which a tear of the thoracic duct was found directly overlying a fracture of the ninth dorsal vertebra. This mechanism of rupture may be aided by fixation of the duct between the tense sharp medial edge of the right crus anteriorly and the vertebral body posteriorly.

Course

The outcome depends possibly on individual architecture of lymph drainage from the cisterna chyli and the extent of the tear in the thoracic duct (Birt and Connolly, 1952).

The symptoms are immediately relieved by thoracentesis but reappear with reaccumulation of fluid. If this persists following repeated thoracentesis it leads to emaciation or even death due to peripheral vascular failure, and drainage on the intrinsic protein reserves (Guest, 1955).

Treatment

Treatment can be dealt with under three headings.

1. *Repeated Thoracenteses*—plus intravenous support, gastric suction and starvation

Approximately half the cases of traumatic chylothorax will recover by repeated thoracenteses alone (Maurer, 1956). In addition, the flow of lymph from the gut may be reduced by putting the gut at rest, to which end starvation and gastric suction have been recommended (Birt and Connolly). In addition, intravenous supportive therapy of various kinds may be used.

In past years the patients who have died following repeated collections of chyle have done so from protein and fat depletion. Chyle is bacteriostatic and only one case of empyema in chylothorax has been reported, Lampson. This suggested transfusing the patient's own chyle after filtering. Little *et al.* (1942) reported several successes using it, but Whitcomb and Scoville (1942) reported a death following such intravenous transfusion.

2. *Phrenic Crush*

This method has been effective in several cases, but has been less favoured since ligature of the duct itself has proved successful. Schnug and Ransahoff were the first to report the successful use of phrenic crush in 1943. They suggested that the raising of the diaphragm which resulted helped to seal the opening in the thoracic duct. Birt and Connolly also report the effective use of phrenic crush.

3. *Ligation of the Thoracic Duct above the Diaphragm*

Before 1948, when the first successful thoracic duct ligation was reported by Lampson, the mortality was 50 per cent., whatever the treatment. In 1950

Meade reported more successes. Goorvitch in 1955 reported 17 patients subjected to ligation of the thoracic duct, all of whom recovered. Since then ligature of the thoracic duct has become routine in persistent chylothorax, but ligation of the duct should not be considered (Meade) until frequent aspirations for as long as two weeks have failed to produce a remission. After this time there is danger of encapsulation of the collapsed lung. The usual approach is through a right thoracotomy. If the actual leak cannot be found the cisterna chyli may have to be ligatured.

Summary

A report of a case of traumatic chylothorax following a closed chest injury is given. The frequency of this condition is discussed. Suggestions are given as to how the actual disruption of the duct occurs. Finally, the accepted lines of treatment are outlined with the success of surgical intervention in cases which require it being emphasised.

I am indebted to Mr. S. W. Holmes, Consultant Surgeon at Mile End Hospital, under whose care this case was originally admitted, for permission to report this case; and to Mr. Belcher, under whose care he was admitted to the Middlesex Hospital. I am especially grateful for his criticism and advice in the writing of this article.

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DIFFUSE INTERSTITIAL PULMONARY FIBROSIS

REPORT OF A CASE

By A. C. Douglas

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The original clinical description of diffuse interstitial pulmonary fibrosis by Hamman and Rich (1944) was of a condition characterised by unremitting dyspnœa progressing to a fatal outcome from respiratory insufficiency or cor pulmonale within six months of the onset of symptoms. It is now apparent that the disorder may be much more chronic, and cases exhibiting histological features essentially similar to those described by Hamman and Rich have been known to survive for as long as nine years after the onset of symptoms (Peabody, Buechner and Anderson, 1953; Wildberger and Barclay, 1955).

The extent and degree of fibrosis is undoubtedly more marked in chronic cases and this might be expected to limit the response shown by these patients to corticosteroids, the only treatment at present available. Such a conclusion would, however, be valid only if the histological changes were known to be uniform in nature and degree throughout the lungs, and lung biopsy, which is sometimes carried out before a decision is made to start treatment with corticosteroids, is often misinterpreted in this respect. A case which illustrates the problem is reported below.

Case Report

Mrs. J.R. æt. 31. During her second pregnancy in 1953 the patient, who had had no previous illness of note, was aware of slight exertional dyspnœa which subsided after confinement. In September 1954, when she was again pregnant, a chest radiograph was taken at the ante-natal clinic because of a persistent unproductive cough. At that time there were streaky opacities in the lower zone of the right lung field, the left hilum was drawn downwards and both hemidiaphragms were elevated. From then onwards she experienced progressively increasing exertional dyspnœa, but until May 1957 was able to dance and even to play tennis, although this made her very breathless. In May 1957 exertional dyspnœa became rapidly worse so that ordinary household duties such as making beds were an effort and she could only with difficulty climb the sixteen stairs in her home. A chest radiograph on 21.5.57 showed a ground-glass appearance throughout the lower two-thirds of both lungs, more marked on the right. Minute dense opacities were also discernible in the mid- and lower zones of both lung fields. Both hemidiaphragms were elevated, though she was not now pregnant, and there was some unfolding of the aorta. Tomography in July demonstrated shrinkage of the left lower lobe and lingula and suggested similar change in the right lower lobe. In October 1957 she was referred to the Northern General Hospital.

On examination she was a well-built, well-nourished young woman with no cyanosis or dyspnœa at rest, no finger clubbing and no lymphadenopathy.

She had slight cough productive of scanty mucoid sputum. The chest, which was normal in shape, moved fairly well on respiration and equally on the two sides. The percussion note was impaired at both bases. The breath sounds were vesicular throughout both lungs with fine crepitations, particularly at the bases.

A chest radiograph on 26.10.57 (Figs. 1 and 2)* showed an increase in the pulmonary opacities on both sides and the unfolding of the aorta was now more in evidence. Bronchography demonstrated marked shrinkage of the left lower lobe and lingula and of the right lower lobe with slight bronchiectatic changes, more conspicuous on the left. Tomography confirmed the unfolding of the aorta and showed that this was not associated with a mediastinal lesion. At screening both hemidiaphragms moved normally in direction on respiration and on sniffing, but excursion was restricted to 1 cm. on the right and 2 cm. on the left. The œsophageal outline was normal. The sputum yielded no specific organism on ordinary culture and six specimens were negative on film and culture for *M. tuberculosis*. The Mantoux reaction was faintly positive to 0·1 ml. of 1 in 1,000 (0·1 mg.) of Old Tuberculin). The erythrocyte sedimentation rate was 11 mm. in the first hour (Westergren). Examination of the peripheral blood showed a hæmoglobin of 94 per cent. and a white cell count of 10,250 per cu. mm., with a normal differential count. The electrocardiogram was normal. Tests of respiratory function gave the following results:

	Actual	*Predicted*
Lung Volumes:		
Total lung capacity	1,790 ml.	4,500 ml.
Vital capacity	720 ml.	3,000 ml.
Inspiratory capacity	520 ml.	2,100 ml.
Expiratory reserve volume	200 ml.	900 ml.
Residual volume	1,070 ml.	1,500 ml.
Intrapulmonary mixing efficiency	40%	>60%
R.V./T.L.C.%	60%	33%
Ventilation:		
Tidal air	400 ml.	
Forced expiratory volume (2 sec.)	630 ml.	2,600 ml.
Maximum voluntary ventilation	23 L/min.	90 L/min.

It was considered that there were two conditions in this patient—the lower lobar and lingular shrinkage, perhaps the result of respiratory infection in childhood, and diffuse pulmonary fibrosis, possibly of the interstitial type. As it was generally believed at this time that corticosteroid therapy in diffuse interstitial pulmonary fibrosis, once begun, should be continued for life, it was decided that the diagnosis should be confirmed by lung biopsy before starting treatment.

Lung biopsy was performed on 21.11.57. At right thoracotomy the parietal surfaces of the upper and lower lobes had a granular appearance. Two wedges were resected, one from the lower margin of the anterior segment of the upper lobe and one from the lateral basal segment of the lower lobe. Both segments

* The figures in the text refer to Plate VI.

had several nodules on their pleural surface. In the removal of the wedge from the lateral basal segment the knife encountered one nodule which was so hard that instead of being divided it was dislodged. It looked like and had the consistency of a spicule of bone.

Microscopic examination was reported as follows:

"The histological picture in both specimens is essentially the same and is dominated by a single outstanding feature—massive hyaline thickening of alveolar walls without any cellular infiltration. Many alveolar spaces have been obliterated, others are mere clefts in a hyaline matrix, others again are cystic structures lined by hyperplastic cuboidal cells (Fig. 3). Masses of free cuboidal cells fill many of the larger alveoli and a few alveoli contain rounded bodies which seem to represent corpora amylacea in various stages of calcification and ossification (Fig. 4). These bodies generally show a distinct pattern of concentric circular markings like those of corpora amylacea, but most of them are ossified to some extent and a few even contain recognisable marrow spaces. A few small thick-walled blood vessels are present."

Several opinions were obtained on the nature of the lung lesion and it was finally concluded that a diagnosis of the Hamman-Rich syndrome was upheld by the pathological picture.

Following operation, and without treatment of any kind, the patient's breathlessness improved and the vital capacity showed a progressive increase from 720 ml. before operation to 1,260 ml. two months later, when the chest radiograph possibly also showed a slight improvement. It was therefore decided to withhold corticosteroid therapy and observe progress. During the next nine months there was a further slight increase in the vital capacity to 1,360 ml., but it was obvious that there had been no further clinical or radiographic improvement.

On 17.10.58 treatment was begun with prednisolone along with antituberculous chemotherapy in the form of PAS and isoniazid. Prednisolone was given in a dose of 40 mg. per day initially with a gradual reduction in dosage to 10 mg. per day given from 29.10.58 onwards. The vital capacity showed a rapid improvement and by 29.10.59 this had increased to 1,890 ml. Improvement continued and one month later the patient felt her breathing had returned to normal. She was now able to dance and do all her housework without difficulty. She could even climb a 1,500 ft. hill near her home and keep up with her companions. The slight cough which had persisted until the introduction of corticosteroid therapy also disappeared. At review on 7.4.59 her general condition was excellent and physical examination of the chest was entirely negative. The vital capacity was 2,500 ml. and the maximum voluntary ventilation was 94 litres per minute. The chest radiograph (Figs. 5 and 6) showed marked clearing in all areas and the hemidiaphragms were now at a normal level, but the minute dense opacities noted in the mid- and lower zones of both lung fields on the initial radiograph were more clearly visible. These almost certainly represented the bone foci discovered at lung biopsy. Treatment with prednisolone (10 mg. per day) is being continued.

Discussion

The most striking histological feature in this case was the presence of bone in the lung lesions. In a paper by Beams and Harmos (1949) mention is made

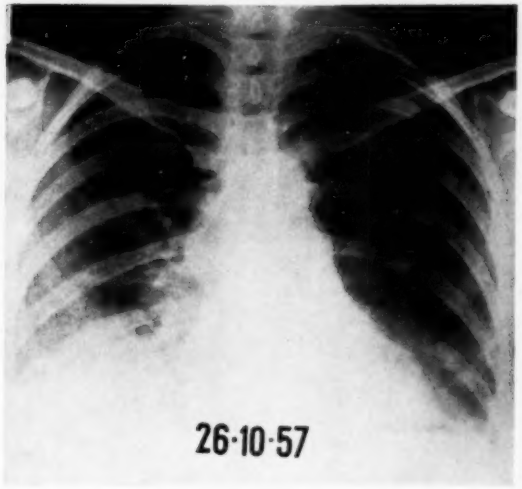

FIG. 1.—Chest radiograph (26.10.57) showing bilateral opacities, mainly in lower zones.

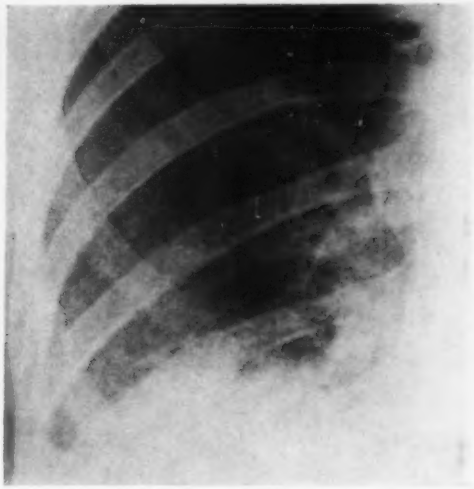

FIG. 2.—Detail from right mid and lower zones (26.10.57) showing minute dense opacities.

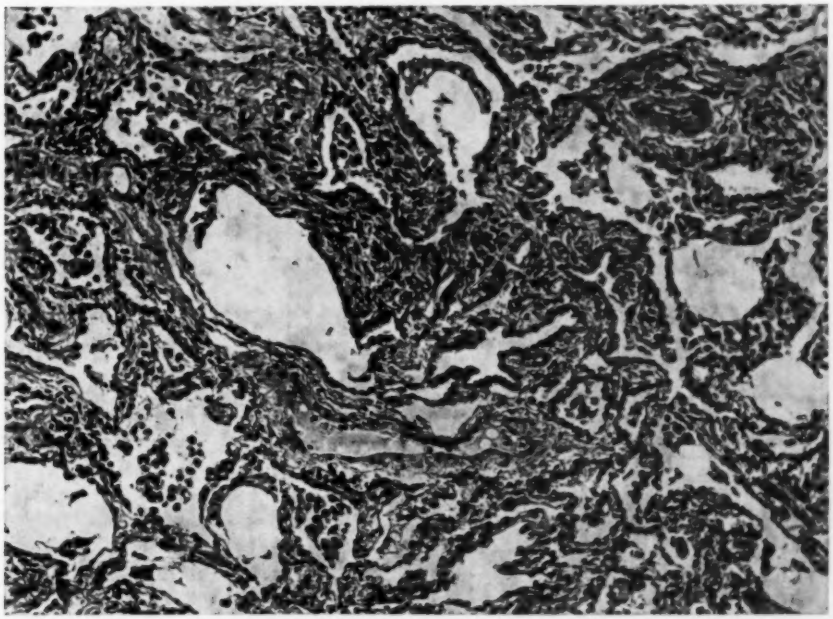

FIG. 3.—Lung section (× 100) showing alveoli of varying size with massive thickening of alveolar walls.

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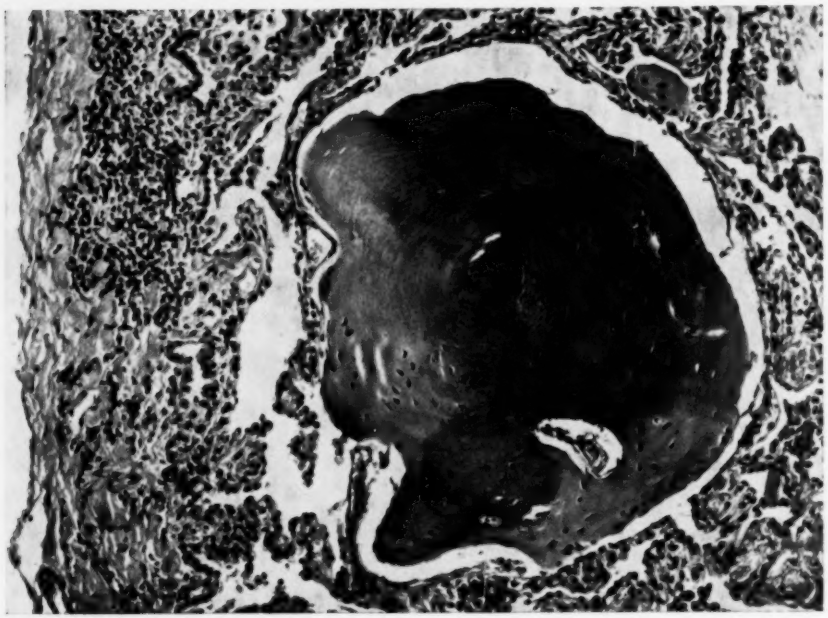

FIG. 4.—Lung section (× 100) showing an ossified body containing a marrow space, within a dilated aveolus.

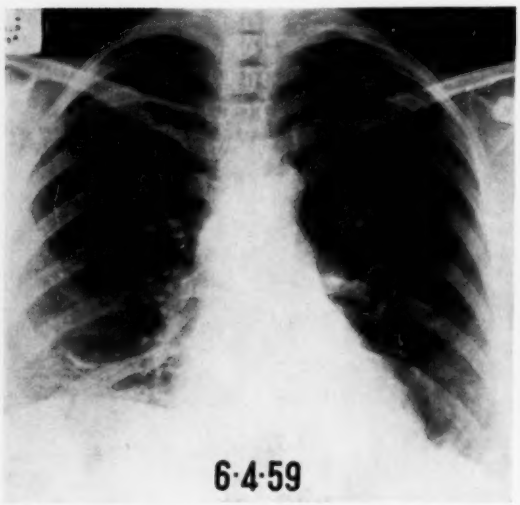

FIG. 5.—Chest radiograph (6.4.59) showing improvement after treatment with prednisolone.

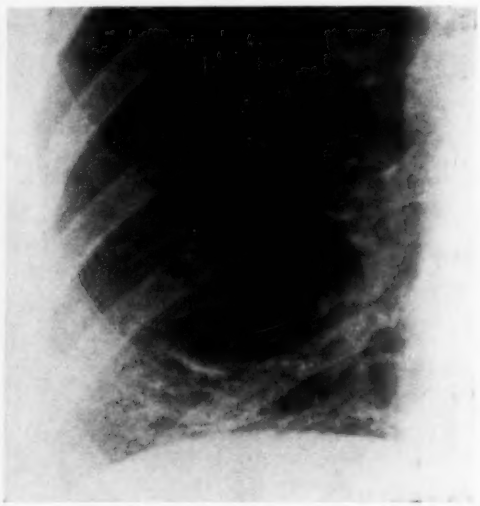

FIG. 6.—Detail from right mid and lower zones (6.4.59) after treatment with prednisolone, confirming improvement but showing residual dense opacities, presumably bone foci.

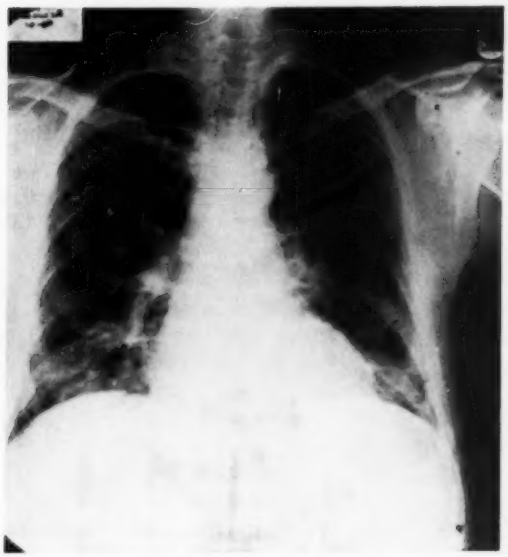

FIG. 1.—Chest radiograph showing patchy opacities in both lower zones.

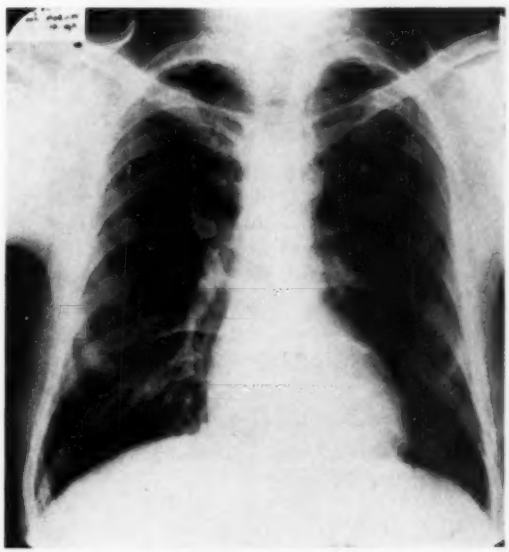

FIG. 2.—Chest radiograph a week later showing clearing of opacities.

of ossification as a pathological feature in diffuse interstitial pulmonary fibrosis, but the reference is a casual one and it is clear that bone formation was not a distinctive feature of the case they described.

Additional points of interest in the present case were the radiographic evidence of shrinkage of the lower lobes and lingula, the improvement in respiratory function which followed thoracotomy, and the response to treatment with corticosteroids. It had been considered that the lower lobar and lingular shrinkage was possibly the consequence of childhood respiratory infection (though there was no historical confirmation of this), but it is interesting to note that similar changes in the left lower lobe were recorded in one of the cases of diffuse interstitial pulmonary fibrosis reported by Grant *et al.* (1956). The improvement in vital capacity after thoracotomy is a further matter for speculation. The theory that the improvement resulted from over-secretion of endogenous cortisone induced by the stress of operation cannot easily be upheld, as improvement continued for several months. Another and perhaps more likely explanation was that the moderate improvement in vital capacity was a consequence of inflation and re-aeration of the lower lobes and lingula by the anæsthetist during the operation.

The most important feature of the case from the practical point of view was the return of respiratory function to a normal level following treatment with prednisolone, in spite of apparently irreversible histological changes, including bone formation, in the lung. The only possible explanation of this apparent paradox is that the changes seen in the biopsy specimen were not representative of the lungs as a whole. This is a possible fallacy in every lung biopsy, and although the procedure is often of great value as a diagnostic measure it seems to be of little help in predicting the therapeutic response to corticosteroids in cases of the so-called Hamman-Rich syndrome.

There remains a further problem for future consideration. The patient is a young woman of 31 who has regained normal respiratory function, and the question arises as to whether treatment with corticosteroids in diffuse interstitial pulmonary fibrosis can ever be stopped with safety. Rapidly fatal deterioration following the withdrawal of corticosteroids in this condition has been reported on several occasions (Schechter, 1953; Peabody, Buechner and Anderson, 1953), and this even when there has been no response to treatment. There has been one case in Edinburgh (Grant, 1959), where severe relapse, occurring after treatment was suddenly stopped by the patient herself, did in fact respond to retreatment with corticosteroids, though even two years later the radiographic appearances had not quite returned to those prior to relapse. The problem of when to stop treatment is not yet solved. It is certain that any attempt to withdraw corticosteroids in the present case will require to be undertaken with the greatest caution and only after a prolonged period of treatment.

Summary

A case of diffuse interstitial pulmonary fibrosis with the unusual feature of bone formation in the lesions is described. In spite of apparently irreversible

histological changes in the lung biopsy there has been a most satisfactory response to treatment with prednisolone.

I wish to thank Professor J. W. Crofton for permission to publish this report, Professor Crofton and Dr. I. W. B. Grant for advice and criticism in the preparation of the paper, Dr. J. M. Drennan for the pathological report, and Miss W. A. M. Tait for secretarial assistance.

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LEPTOSPIROSIS CANICOLA PRESENTING AS PNEUMONIA

By D. H. A. Boyd

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In Great Britain canicola fever is a relatively uncommon disease. Nevertheless the symptoms and the course of the illness are well known and it is evident that involvement of the respiratory system is rare. For this reason the following case is of interest.

Case Report

A previously healthy 41-year-old coal miner became ill a week before admission to hospital with headache, fever and sore throat. Two days later he developed an unproductive cough and was given penicillin orally. During the next forty-eight hours he felt better and his temperature became normal, but pyrexia then returned and was accompanied by vomiting. Despite chlortetracycline by mouth he did not improve and, on examination, dullness to percussion and diminished air entry and crepitations at both lung bases were noted.

When admitted to hospital on the eighth day of illness he was lethargic and complained of moderately severe headache. Pyrexia of 103° F. was present, but no abnormality apart from coarse crepitations at both bases was found on clinical examination. The white cell count was 9,800/c. mm., erythrocyte sedimentation rate (E.S.R.) Westergren 21 mm. in one hour, and hæmoglobin 90 per cent. (Sahli). A chest radiograph showed patchy opacities, mainly in both lower zones (Fig. 1).*

The following day nuchal rigidity and conjunctival injection were present. In view of his occupation a diagnosis of leptospirosis icterohæmorrhagica was considered, but it was also learned that a pet dog had recently become ill. Subsequent investigations gave the following results: Cerebro-spinal fluid (C.S.F.): cells 244/c. mm. (neutrophil polymorphs 81 per cent., lymphocytes 19 per cent.), protein, sugar and chlorides normal, sterile on culture. Urine: protein +, bile-trace, pus cells + and red blood cells +, no leptospira seen by dark-ground microscopy. Blood: culture for leptospira negative, agglutination reactions for *Leptospira canicola* positive only to a titre of 1/10, but positive to a titre of 1/30,000 ten days later. Liver function tests and blood urea were normal.

Treatment with crystalline penicillin 8 mega units daily by injection was started and continued for two weeks. He became afebrile in forty-eight hours and made a rapid and complete recovery. The chest radiograph became normal (Fig. 2). The pet dog which was examined at the Royal (Dick) Veterinary College, Edinburgh, was found to be excreting *L. canicola* in its urine. Other members of the family (the patient's wife and four children) remained well and their serum failed to agglutinate *L. canicola*.

* The figure numbers in the text refer to Plate VIII.

(*Received for publication September* 15, 1959.)

histological changes in the lung biopsy there has been a most satisfactory response to treatment with prednisolone.

I wish to thank Professor J. W. Crofton for permission to publish this report, Professor Crofton and Dr. I. W. B. Grant for advice and criticism in the preparation of the paper, Dr. J. M. Drennan for the pathological report, and Miss W. A. M. Tait for secretarial assistance.

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Brit. J. Dis. Chest (1960) **54**, 91.

LEPTOSPIROSIS CANICOLA PRESENTING AS PNEUMONIA

By D. H. A. Boyd

From the Respiratory Diseases Unit, Northern General Hospital, Edinburgh

In Great Britain canicola fever is a relatively uncommon disease. Nevertheless the symptoms and the course of the illness are well known and it is evident that involvement of the respiratory system is rare. For this reason the following case is of interest.

Case Report

A previously healthy 41-year-old coal miner became ill a week before admission to hospital with headache, fever and sore throat. Two days later he developed an unproductive cough and was given penicillin orally. During the next forty-eight hours he felt better and his temperature became normal, but pyrexia then returned and was accompanied by vomiting. Despite chlortetracycline by mouth he did not improve and, on examination, dullness to percussion and diminished air entry and crepitations at both lung bases were noted.

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The following day nuchal rigidity and conjunctival injection were present. In view of his occupation a diagnosis of leptospirosis icterohæmorrhagica was considered, but it was also learned that a pet dog had recently become ill. Subsequent investigations gave the following results: Cerebro-spinal fluid (C.S.F.): cells 244/c. mm. (neutrophil polymorphs 81 per cent., lymphocytes 19 per cent.), protein, sugar and chlorides normal, sterile on culture. Urine: protein +, bile-trace, pus cells + and red blood cells +, no leptospira seen by dark-ground microscopy. Blood: culture for leptospira negative, agglutination reactions for *Leptospira canicola* positive only to a titre of 1/10, but positive to a titre of 1/30,000 ten days later. Liver function tests and blood urea were normal.

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(*Received for publication September* 15, 1959.)

Discussion

In severe forms of leptospirosis such as Weil's disease there may be involvement of the respiratory system leading to bronchitis or bronchopneumonia, sometimes associated with blood-stained sputum. These are infrequent clinical findings and are uncommonly reported at autopsy (Alston and Broom, 1958).

Fatal cases of human canicola fever are extremely rare. Autopsy reports from the only two well-authenticated cases (Wolff and others, 1951; Weetch and others, 1949) mention petechial hæmorrhages in the pleura in one case in which jaundice was present. This case also had œdematous lungs which microscopically contained small foci of bronchopneumonia which was considered to be terminal. Occasionally during the course of the illness " congestion of the lungs " is noted, but pneumonia has not been demonstrated radiographically in canicola fever. Although Ayala (1948) reported a case of Weil's disease with hæmoptysis and pulmonary opacities on a chest radiograph, there are grounds for doubt, from the clinical description of the case, whether the respiratory symptoms were entirely explicable on the basis of leptospiral infection.

Although no proof can be offered, it seems reasonable to assume that the pneumonia in the case described here was due to *L. canicola*.

Summary

A case of presumed human canicola fever presenting as pneumonia is described, and it is suggested that the pneumonia in this case was due to *L. canicola*.

I wish to thank Dr. I. W. B. Grant for permission to publish this case.

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Brit. J. Dis. Chest. (1960) **54**, 93.

REVIEWS OF BOOKS

Modern Trends in Diseases of the Vertebral Column. REGINALD NASSIM and H. JACKSON BURROWS. (Butterworth's Modern Trends Series.) Butterworth and Co. Pp. 292. Illus. 75s.

The editors point out that this book is written on an anatomical basis, and remind the reader that bone changes may be an early indication of generalised disease. For this reason the book should "appeal to a wide circle of the medical profession." One is impressed by the enormous amount of care that has been taken both in the layout and subject matter. The reproduction is excellent throughout.

The opening chapters on anatomy and on congenital abnormalities are particularly useful to the orthopædic surgeon interested in the problems of disc degeneration, or in the ætiology of spondylolisthesis. There follows an excellent chapter on scoliosis.

The physician will find interest in the chapters on spinal osteoporosis, cervical spondylosis and tuberculous disease of the spine. This last is written by one who has had many years' experience in the treatment of bone and joint tuberculosis. That he has managed to condense into four and a half pages all the essentials of diagnosis and treatment of the tuberculous spine is greatly to his credit, and the essentials are all there. Yet, if the reader is left with a feeling that something is missing, he must remember that the title of the book is "Modern Trends" and that the chapter is not intended to be a complete description of the disease. The section on surgical treatment may offer a new line of approach to some readers, but the author is rightly reserved in his assessment of the end results of these new methods.

Perhaps a few lines might have been devoted to the value of treatment in a long stay hospital on physical and educational grounds, and a little more said about the complications of prolonged recumbency, *e.g.* renal calculi, and the value of open-air treatment, or perhaps this is out of date. Interest in bone tuberculosis is declining in this country, but it is well to remember that in other countries the disease is still a major problem.

When a number of authors contribute to the whole, a certain amount of repetition is inevitable and in fact desirable, but the editors have managed to produce an astonishing degree of harmony throughout this excellent work.

H. L. C. WOOD.

Peripheral Vascular Diseases. By TRAVIS WINSOR. Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. xviii +845. Illustrated. £6 5s.

Dr. Winsor's comprehensive treatise on peripheral vascular disease is divided into two main parts. The first part covers anatomy, function and techniques of investigation of the peripheral vessels, with nearly 100 pages devoted to plethysmography, in addition to a chapter on pressure transducers.

The second part deals with the history, physical examination and classification of peripheral vascular diseases, which are described individually. The last chapter covers treatment, including the latest surgical techniques.

There are chapters on the ætiology of atherosclerosis and blood coagulation.

The book is profusely illustrated with black-and-white drawings, which in many instances are ingeniously designed and of obvious value, but the overall impression gained is that the text has been sacrificed to the illustrations, for the former in some places is almost telegraphic in style. Arterial grafting is discussed in half a page, and although there are numerous references to the bibliography, no balanced summing up of the value and results is given in the text, which therefore tends towards dogmatism. Mitral valvotomy is not mentioned in the prevention of systemic emboli in mitral valve disease in the chapter on systemic embolism. The chapter on neurovascular syndromes of the upper extremities is readable and comprehensive, however, and typical of many parts of the book.

For the reader who requires a comprehensive book on the peripheral vascular system, Dr. Winsor's work can certainly be recommended, but the concentration on methods of diagnosis tends to make it somewhat top-heavy, and more attention to the commoner disorders at the expense of the discussion of minor and rare conditions would be welcomed.

J. F. GOODWIN.

Cardiovascular Sound in Health and Disease. By VICTOR A. MCKUSICK. Baltimore: Williams and Wilkins Company. London: Baillière, Tindall and Cox. 1958. Pp. 570. Illustrated.

This textbook is a comprehensive study of the production of sounds by the heart and great vessels in health and disease. Beginning with a fascinating survey on the history of cardiovascular sound, the author then deals with the fundamentals of the nature of sound, the art of auscultation, and the practice of phonocardiography. Both conventional (oscillographic) phonocardiography and spectral phonocardiography are described in detail. Throughout the book frequent reference is made to the latter technique (in which the frequency spectrum of the sounds is portrayed), but conventional phonocardiograms are also illustrated profusely. Passing reference is also made to intracardiac phonocardiography. There is a chapter on the structure and function of heart valves, temporal relationships of heart sounds and electrical and mechanical phenomena in the heart, and on the generation of sound within the cardiovascular system.

The second half of the book is devoted to cardiovascular sound in disease; abnormal sounds and murmurs are intensively studied and related to anatomical, hæmodynamic and radiological data.

The final chapters deal with cardiovascular sound in animals, lung sounds, and technical problems of recording.

There is an extensive bibliography, and the illustrations are profuse and, with a few exceptions, of excellent quality. There are some admirable photographs of pathological specimens and useful tables of the timing of auscultatory events in various disorders have been included.

The author's style is pleasing and frequent reference is made to the work of others, while every attempt has been made to support conclusions with accurate data. Abbreviations, however, are perhaps too frequently used in the text.

Dr. McKusick is to be congratulated on producing a book which will have an immediate place as a work of reference, and should provide fascinating and important reading for cardiologists.

J. F. GOODWIN.

Acta Tuberculosea Scandinavica, Supplementum XLIV. Long-term Prognosis in Pulmonary Tuberculosis detected by Mass Radiography. By IVAR KÄLLQVIST. Copenhagen: Ejnar Munksgaard. 1958. Pp. 177; 55 tables, 31 figures.

Between October 1946 and January 1949 a M.M.R. survey was carried out in Södermanland County, Sweden, in which 96·7 per cent. of the population over 7 years of age were X-rayed. The actual number attending for X-ray was 178,344, of which 13,905 showed healed lesions; 5,667 manifested lesions requiring further investigation; and 676 were finally considered to be notifiable cases of tuberculosis, and therefore placed on the register. In addition to these, 292 cases of pulmonary tuberculosis were discovered during the period of the survey but independently of the M.M.R. campaign (*i.e.* symptom group or contact cases, etc.), and these were regarded as controls for prognostic comparisons with the M.M.R. group.

In general, the prognosis was demonstrated to be better in the Survey Cases than in the Control Cases. Thus, for example, 73 per cent. of the controls were initially classified as advanced or moderately advanced as against 59 per cent. of the survey cases; and excavation was noted in 45 per cent. of the controls as against 21 per cent. of the survey cases.

Of the cases judged to be *initially active* (339 survey and 248 controls) X-ray progression or retrogression was roughly the same in both groups, except for the far advanced cases which progressed more frequently in the controls. Mortality, therefore, was higher in the controls, of which 21 per cent. died in the first year of observation as against 4 per cent. of the survey cases. After eight years' follow-up 29 per cent. of the controls had died as against 12 per cent. of the survey series.

Some of the cases judged to be *initially inactive* relapsed later. The overall figures for survey and controls combined showed a 4 per cent. relapse in five years and an 8 per cent. relapse in eight years, indicating the necessity for adequate follow-up of all cases.

A second M.M.R. survey involving 96·8 per cent. of the population was carried out in 1953-55, *i.e.* five years after the first. In the first survey the newly discovered active cases amounted to 1·9/1,000 of the population. In the second survey the figure was 1·1/1,000. The proportion of far advanced cases amongst those discovered in the first survey was 17·1 per cent. as against 8·3 per cent. in the second. In the second survey there was a pronounced shift towards the higher age groups in the male cases.

The above are a few of the points emerging from a very comprehensive study, which the interested reader would do well to examine in detail.

CHRISTOPHER CLAYSON.

Das Röntgenschichtbild. By A. GEBAUER, E. MUNTEAN, E. STUTZ, and H. VIETEN. Stuttgart: Georg Thieme. 1959. Pp. 454+xvi; 699 illustrations. DM.148.

This is a survey by four German authors of the scope of tomography in radiodiagnosis. It attempts to be exhaustive in range, and inevitably the emphasis and treatment are rather uneven. A lengthy account of the theoretical geometrical principles of the method is followed by applications in the skull, the skeleton, the larynx, the thorax, the abdomen, and there is an unworthy and perfunctory couple of pages on the nervous system.

Well over half the book is devoted to the thorax and its organs. Stress is laid on the use of body section stratigraphy as the third dimension in tomography, and numerous illustrations compare the appearances that may be found in the three basic tomographic planes, coronal, sagittal, and cross-section. There is a good account of the normal appearances of the thorax in body section films, with accompanying illustrations of corresponding anatomical preparations. This is a useful and necessary prelude to the discussion of the technique. A similar excellent section compares conventional tomographs of the petrous bone of the dry isolated bone of the skull and those obtained in the living subject with anatomical cross-sections through the bone itself.

It is clear that tomography as a method is most successful when combined with contrast examinations, such as bronchography or retro-peritoneal gas insufflation, to obtain the maximum delineation between anatomical structures. The most interesting section of the book is that devoted to tomography following an induced pneumo-mediastinum, a method developed by Condorelli of Rome, whose illustrations are used. The value of body section stratigraphy (apart from its use in planning radiotherapy courses) does not seem to be commensurate with its difficulties, both in obtaining and interpreting.

The book is excellently produced and lavishly illustrated, and a great majority of the illustrations succeed in making the point intended. In general, any book devoted to one single technique of examination must seem somewhat limited and haphazard in its approach; this volume does not altogether escape the danger, but is on the whole a worthy and industrious compilation which gives a clear illustration of the potentialities of the method.

R. EBAN.

Bronchial Asthma—A Symposium. Report of a meeting held on February 25, 1959, at the Royal Society of Medicine. London: The Chest and Heart Association. Pp. 96.

The degree of disabling crippledom created by asthma makes a comprehensive symposium such as this by experts in this field particularly timely. Every aspect of the subject is well considered, with a view to effective management of the condition itself. Allergy and infection, physiological considerations and psychological aspects, the use of steroids, home management, and suggestion and hypnosis in the treatment of the disease, are all recognised and assessed.

The booklet can be highly recommended, is well produced and illustrated, and should be of value to all those interested in this widespread disease.

Brompton Hospital Reports. Vol. 27, 1958. London: Published for the Research Department of the Hospital by Lloyd-Luke (Medical Books) Ltd. Pp. 276. Price 15s.

Volume 27 of the Brompton Hospital Reports comprises a series of papers published in the medical press. They all reach the usual high standard of this series and it is invidious to single out any particular article. All branches of intra-thoracic medicine are covered, including diseases of the heart, lungs and œsophagus, and there are also contributions on various aspects of tuberculosis. Some of the contributions are, however, of particular interest. In the sphere of heart disease the problem of "restenosis of the mitral valve"

following valvotomy for mitral stenosis by Belcher, the subject of "aortic stenosis" by Wood, and "cardiac syncope in atrial septal defect" by Papp, are reviewed comprehensively. The report of twenty-four cases of pleural neoplasm, including histology, and a very complete description of the clinical syndrome with a consideration of the origin of these tumours, is admirably discussed by Smart and Hinson, and the paper on "pulmonary mycoses" in Britain, by Riddell and Clayton, is an excellent review of this increasingly important subject.

The editors are to be congratulated once again on producing a volume so satisfying mentally and physically.

PHILIP ELLMAN.

Robert Koch: Briefe an Wilhelm Kolle. Edited by KURT KOLLE, Professor of Psychiatry and Neurology in Munich, with introduction by GEORG B. GRUBER, Professor of Pathology in Göttingen. Stuttgart: Georg Thieme Verlag, 1959. Pp. 67. Illustrated.

This collection of letters throws fresh light on the character and personality of Robert Koch. It reveals a human and sympathetic aspect in the man who hitherto has been chiefly known as a sun in the scientific firmament, the discoverer of the tubercle bacillus and a pioneer in immune-therapy. The correspondence has been edited by Professor Kurt Kolle, son of Professor Wilhelm Kolle to whom twenty-four of the twenty-eight letters are addressed.

The first four letters in this book, written about 1858, tell of Koch's first love. Frau Marie Goedicke, whom he always called *Liebe Tante*, was his confidant and adviser in the difficulties of his school days and the stresses of his adolescence. At the age of 15 he wanted to marry Frau Goedicke's daughter Agatha. The mother told them they were both too young and the romantic youth had to acquiesce. But he retained a soft spot in his heart for Agatha, who married Albert Kolle. The Koch and the Kolle families were close friends. When Agatha's son, Wilhelm Kolle, had qualified in medicine, she wrote to Koch, now great and famous, and he took him as his assistant in Berlin.

In 1896 Koch was asked by the British Government to investigate rinderpest, the cattle plague in South Africa. In 1865 Burdon-Sanderson, working for the Experimental Committee of the Royal Commission on Cattle Plague, had written a report on the subject which Koch said was the best ætiological and pathological study that had been made. Burdon-Sanderson noted that the infective agent did not diffuse through parchment paper, which led him to suspect that it was ultra-microscopic. It is now known to be a virus.

Hardly had Koch embarked upon his research into rinderpest when bubonic plague broke out in India and the British Government begged Koch to go there. He nominated Wilhelm Kolle as his successor to complete the rinderpest investigation. Eventually, Kolle also succeeded him as Director of the Berlin Institute for Infectious Diseases. Koch's letters to Kolle from 1896 to 1908 are full of scientific information and suggestions for research, and also show a most friendly relationship between master and pupil. Koch found in Kolle a worthy disciple, but never forgot that he was Agatha's son. As late as 1909 he wrote to her as *Liebe Agathe!*

ARTHUR S. MACNALTY.

Die Streifenatelektasen der Lunge. Priv.-Doz. Dr.Med. FRIEDRICH HEUCK. Stuttgart: Georg Thieme. Pp. 108. Illus. DM.32.

In 1936 Fleischner first described the narrow opacities at the lung bases which have come to be known as linear atelectasis, and was able to bring forward evidence that they were indeed due to collapse. Since then the appearance (and frequently rapid disappearance) of these shadows has puzzled and tantalised physicians and radiologists alike. It has often seemed difficult to accept the segmental nature of these lesions, or that they are due to collapse.

The little monograph by Dr. Heuck is, therefore, welcome. He has examined a considerable number of such cases both clinically and radiologically. After a description of this phenomenon he presents a detailed bibliography of the subject. This is followed by a consideration of the pulmonary subsegments, and it is shown how most of these opacities fit into the subsegmental pattern. Others, less obliging, are usually associated with a raised diaphragm, and Dr. Heuck shows ingeniously how these appearances can be imitated experimentally by compressions of water-containing non-homogeneous sponge. He regards some of the cases in question as compression zones in waterlogged lungs.

The monograph is less convincing when its author tries to establish the mechanism of collapse. He shows that the bronchi in the segment need not necessarily be occluded, and by means of animal experiments examines the influence of the vegetative nervous system on pulmonary muscle and blood flow. This part of the work, though interesting, is inconclusive.

The work will be of interest both to radiologists and chest physicians. The illustrations are of the highest order, and the production of the book is up to the standard of the Georg Thieme Verlag.

F. STARER.

Handbuch der Urologie. Bd. 9/2. Inflammation II. Editors: C. E. ALKEN, V. W. DIX, H. M. WEYRAUCH and E. WILDBOLZ. Berlin: Springer. Illus. Pp. 564.

Volume IX/2 of the Encyclopædia of Urology is devoted to Specific Inflammations. There are three parts: Urogenital Tuberculosis; Parasitic Infections of the Genito-Urinary Tract; and a group containing Syphilis, Lymphogranuloma Venereum, Granuloma Inguinale and Chancroid (but not Gonorrhœa).

The first part, written mainly by Einar Ljunggren, is of most interest to the urologist. The present time, eighty years after Cohnheim and thirty since the previous edition of the Encyclopædia, is a most convenient one from which to survey the methods of the past—the pre-chemotherapeutic age—and the future, in which we hope that surgery will only be required to correct minor complications of medical treatment. There are references to most of the main publications, and where there is a difference of opinion this is clearly stated. There are no less than thirty-one pages of lists of references, one author having over fifty page references.

There are few illustrations and these are unequal in value. Some of the photomicrographs are of poor quality (there should be no place for blurred low-power views in a book like this), but others are very good. Misprints are very rare.

The second part is devoted to Parasitic Infections and is written in a delightful style by R. Campbell Begg. He describes, among other diseases, Schistosomiasis in an unforgettable manner. "The muscular midget loops along in the vessels"—and his coloured plates of cystoscopic appearances are excellent. The tropical and subtropical diseases are bound to figure more largely in Urology in future, and it is to be hoped that the scarring caused by the schistosomes will be avoided in future generations.

It is interesting to have proof that some of the legends of our boyhood are supported by scientific data—there *is* a fish which enters the urethræ of bathers —and its name is Candiru.

Finally, Ambrose King has collected a most impressive list of papers on some venereal conditions—syphilis does not seem to be quite the scourge it might be, and the others, we hope also, will not cause many urological headaches.

A. R. C. HIGHAM.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

Automatic Ventilation of the Lungs. By Wm. W. Mushin, L. Rendell-Baker and Peter W. Thompson. Oxford: Blackwell Scientific Publications. Pp. 349, illus. 47s. 6d.

Transactions of the 17th Conference on the Chemotherapy of Tuberculosis, 1958. VA Dept. of Medicine and Surgery, Central Office, Washington, The Atlanta Area Medical Office and the VA (MTG) Hospital, Memphis, Tenn. Pp. 513.

Transactions of the 18th Conference on the Chemotherapy of Tuberculosis, 1959. The VA Dept. of Medicine and Surgery, Central Office, Washington, D.C., and the St. Louis Area Medical Office.

Brit. J. Dis. Chest. (1960) **54**, 100.

REPORTS

BRITISH STUDENT TUBERCULOSIS FOUNDATION

THE several Units of the British Student Tuberculosis Foundation have now been brought together to form a permanent centre for the treatment and rehabilitation of students with tuberculosis at Pinewood Hospital, Wokingham, Berkshire. Both men and women students are admitted to the Combined Student Unit, which has thirty-two beds available for student patients. Treatment is provided at Pinewood for students from the first diagnosis of their tuberculosis until they are ready for final discharge from hospital.

In the Student Centre at Pinewood students may receive medical treatment under the National Health Service while they continue to work in their chosen field, and, in some cases, take their examinations. The academic and social facilities provided by the British Student Tuberculosis Foundation are available to men and women students alike. The Library has over 3,000 books, both works of reference and general literature, while for convalescent patients there are seven separate studies for private work.

It is the essence of the academic work at Pinewood that students should be able to continue with their studies with as little interruption as possible from the time of diagnosis. Experience at the Student Unit has shown that the interruption a student suffers in his study can be minimised without detriment to the health of the patient. The academic needs of each student are assisted with advice from his own University or College tutors and he works with one or more tutors, who are responsible for seeing him regularly and directing his work. The combination of the medical treatment under the supervision of Dr. J. J. McCann, M.B., M.R.C.P., and of the educational facilities of the Foundation, provides a unique opportunity for reducing wastage of time to a minimum.

Enquiries concerning the admission of student patients to the Student Centre should be addressed to the Secretary/Administrator, British Student Tuberculosis Foundation, Pinewood Hospital, Wokingham, Berkshire.

THE CHIEF MEDICAL OFFICER'S ANNUAL REVIEW FOR 1958*

UNTIL means are found of preventing or improving the treatment of cancer and degenerative diseases of the circulatory system the present expectation of life is not likely to be appreciably extended, declares Sir John Charles, Chief Medical Officer of the Ministry of Health, in his review of 1958 from which we quote certain relevant aspects of interest to our readers.

The expectation of life in England and Wales has remained practically constant over the past five years, though the proportion of persons over 65 years of age has risen slightly from 117 per 1,000 in 1957 to 118 per 1,000 in 1958. Diseases of the circulatory system now account for over one-third of the total deaths, and second in the hierarchy of destruction are the cancers, accounting for about one-sixth. There is as yet little sign of any halt in the rising trend shown by cancer of the lung deaths over past years.

* Report of the Ministry of Health for the year 1958. Part II: "On the State of the Public Health," being the annual report of the Chief Medical Officer. Command 871. H.M.S.O. 12s. net.

The Respiratory Viruses

Diseases of the respiratory system constitute the commonest group of illnesses in England and Wales. *The common cold* was found (in a report from general practice) to have the highest patient casualty rate of all the individually listed diseases, and the distribution of illnesses by diagnostic groups showed that 23·1 per cent. were classified as diseases of the respiratory system.

It cannot yet be claimed that any virus, which can be recognised by laboratory tests, has been shown to cause the ordinary common cold, although illnesses resembling the common cold may fall within the range of clinical manifestations of infections with viruses of the influenza and para-influenza groups. Experimental work on the common cold virus has of necessity been based largely on human transmission studies.

Sir John Charles, summing up the present state of knowledge concerning viruses as ætiological factors in diseases of the respiratory system, states that " the immediate prospects of unravelling this complex group of illnesses have seldom appeared brighter. The multiplicity of agents which are being brought to light through recent advances in laboratory techniques make it appear probable that among these agents may be found some which are responsible for the commoner forms of respiratory illness . . . the need for the continuation of human transmission studies has, if anything, been enhanced by the progress achieved in the laboratory. The practical importance of arriving at a more precise differentiation of the common respiratory diseases needs little emphasis. The recurrent epidemics which are a regular feature of the English winter are undoubtedly of mixed origin, but, apart from influenza virus infections, the bulk of the respiratory illnesses cannot be assigned to any known cause."

Tuberculosis Detection

Deaths from all forms of *tuberculosis* in 1948 numbered 21,993—19,088 from pulmonary and 2,905 from other forms. Ten years later the total was 4,480 of which 3,999 were due to pulmonary tuberculosis and 481 to other forms. These figures show how striking is the overall improvement, but even more remarkable is the improvement in the younger age groups. In young women between the ages of 15 and 30 the death rate is less than 3 per cent. that of 1948, and for young men in the same age group it is less than 4 per cent. In both sexes below this age the present rate is less than 5 per cent. of that prevailing ten years ago. But as the age scale is ascended the fall in death rates is less distinct. This is to be expected since many of those now dying of tuberculosis in the fullness of age are succumbing to infection acquired in their early years which has long been dormant or mainly so and has only now been reactivated in the weakening process associated with ageing. For all ages and both sexes the death rate per million for respiratory tuberculosis is now approximately one-fifth of those ten years ago.

Since the peak of 1954 when 8,728 cases of pulmonary tuberculosis were found by the Mass Radiography Service the number of cases has been falling. In 1957 (the most recent figures available) 3,154,600, about 103,000 more than in 1956, were X-rayed, and the number of cases actually found was 6,481, or 1·8 per 1,000.

" Hitherto," comments the Chief Medical Officer, " mass radiography has been, as its name implies, largely a matter of X-raying as many volunteers as

possible, and in the early days that was undoubtedly the right objective since the case rate was, on the average, over 3 per 1,000. As the rate continues to decline mass radiography should become still more selective and still more closely integrated with the other chest and radiological services. It may be that a more appropriate designation for it would be selective group radiography.

During the year an average of 262 people died daily from *malignant disease* and of these 54 died of *cancer of the lung*. By comparison accidents caused by motor vehicles were responsible for 15 deaths a day and tuberculosis for 12 deaths a day.

The lung cancer death rate per million living continues to increase in both sexes, but there is some evidence that the rate of increase is slowing down. The ratio of the male to the female death rate is now 6·6 to 1, but it is significant that it is the over-50 age group only that is responsible for the increasing ratio. This is what might be expected to occur if cigarette smoking were a major causative factor.

Public Health

The Chief Medical Officer emphasises that "one of the natural results of the formation of the present National Health Service will be the inevitable development of greater co-operation between the hospital, the practitioner and the public health services . . . the illness or disability of the hospital patient does not begin at the time of his admission, nor does it necessarily end when he leaves. And since health departments are becoming increasingly concerned with domiciliary care and after-care, they share a common ground with the family physician. Tripartite as the national health service may seem to be, it is, in essence, one service. . . . Each of these three divisions is complementary to the other, and each must be envisaged in the wide setting of the service as a whole."

INTERNATIONAL TUBERCULOSIS CONFERENCE AT ISTANBUL (1959)

Dr. M. M. Nagley attended the 15th International Tuberculosis Conference held in Istanbul from September 11-19, 1959, under the auspices of the International Union against Tuberculosis, and reports that it followed the one in New Delhi of January 1957, and, so far as the scientific sessions were concerned, the Istanbul conference was the logical conclusion of the former meeting, in that all the sessions were planned on the symposium basis. That is to say, several subjects were chosen, each of which was of broad spectrum and was handled by the Chairman or "Moderator," flanked on the platform by many main speakers who spoke on the particular facets of the subject in hand and in the form of—for the main part—a panel discussion. The subjects chosen were:

(1) Chemoprophylaxis of tuberculosis.
(2) The problem of atypical mycobacteria.
(3) Present-day indications of surgical treatment of pulmonary tuberculosis.
(4) New antibacterial drugs.
(5) Relapse after treatment (medical and surgical).
(6) Health Education and new methods of prevention and treatment of tuberculosis.
(7) The role of the Public Health Nurse and the Social Services.
(8) B.C.G. vaccination and immunity.

During the progress of the conference several similar sessions took place, dealing with main points and aspects of the subject such as, for instance, a trial of Cycloserine.

Your correspondent felt on the whole that the panel sessions and the scientific sessions hindered rather than helped the acquiring of knowledge at the conference, but, although the ultimate outcome was disappointing, a great deal of new and interesting material was presented. In the chemoprophylaxis of tuberculosis, for instance, the giving of drugs to individuals who had not been previously infected had been separated from those who had been so infected with tuberculosis, thus coining the words " Chemoprevention and Chemoprophylaxis." It seemed to be the spirit of the session that Chemoprophylaxis was a form of therapy of the future and the work of Schmidt on Simian tuberculosis with particular reference to Isoniazid and the use of Isoniazid-resistant BCG provoked stimulating discussions.

There could be little doubt that atypical acid-fast bacilli were rearing their heads in American Chest Disease practice, and the division of these bacteria into photo-chromogenic and scoto-chromogenic types was well substantiated and discussed. It was interesting that these atypical bacteria had quite a long history in the U.S.S.R., where it was generally agreed that they were a manifestation of the variability of the *Bacillus tuberculosis*.

The discussion of new antibacterial drugs was perhaps the most disappointing in that, with the noticeable exception of 1314, nothing seemed to be particularly new and the serious problem of the type of chemotherapy to use in patients whose bacteria are resistant to two of the three standard agents still remains to be answered.

The session devoted to the surgical management of pulmonary tuberculosis was most ably moderated by Sir Clement Price Thomas, who dealt in a very statesmanlike fashion with the many varying points of view regarding the relative merits of surgical collapse therapy and surgical resection. One had clearer ideas at the end of this session of indications for surgical treatment than about the subjects at the end of other sessions, but even here there was a welter of material discussed and a variation of the criteria of assessment which renders it difficult to state conclusions except to say that resectional surgery seemed to be being delayed longer than formerly in favour of chemotherapy, and that surgical collapse was still being carried out in many countries of the world.

The work of the Medical Research Council in Great Britain in the field of BCG was carefully outlined and received with the utmost respect, as was the work from India which suggested that some vaccinations with BCG had offered less protection than was originally thought, in low tuberculin sensitivity areas.

From the moment of the opening of the Conference by the President of the Council of Ministers, Mr. Menderes, to the final word being spoken, the scientific sessions and social arrangements of the conference were enjoyed by many and the hospitality shown by the President of the International Union, Professor Saglam of Turkey, and his organising committee was outstanding, in that the visitors were enabled to see as much of Istanbul as possible in so short a time and to meet and talk informally in large rooms adjacent to the conference, with colleagues from all over the world.

The next conference of the International Union against Tuberculosis will be held in Canada in 1961. It is being eagerly awaited by those who were in Turkey.

Brit. J. Dis. Chest. (1960) **54**, 104.

NOTES AND NOTICES

THE THORACIC SOCIETY

The Thoracic Society is holding meetings in 1960 on the following dates:

Spring Meeting in London on 11th and 12th March.
Summer Meeting in Edinburgh on 15th and 16th July.

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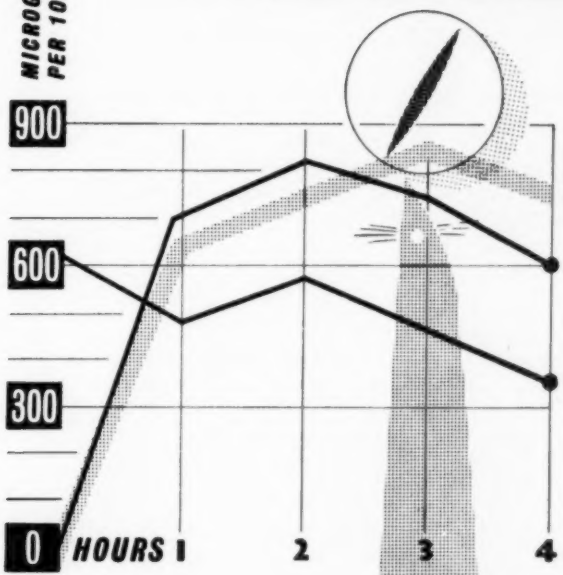

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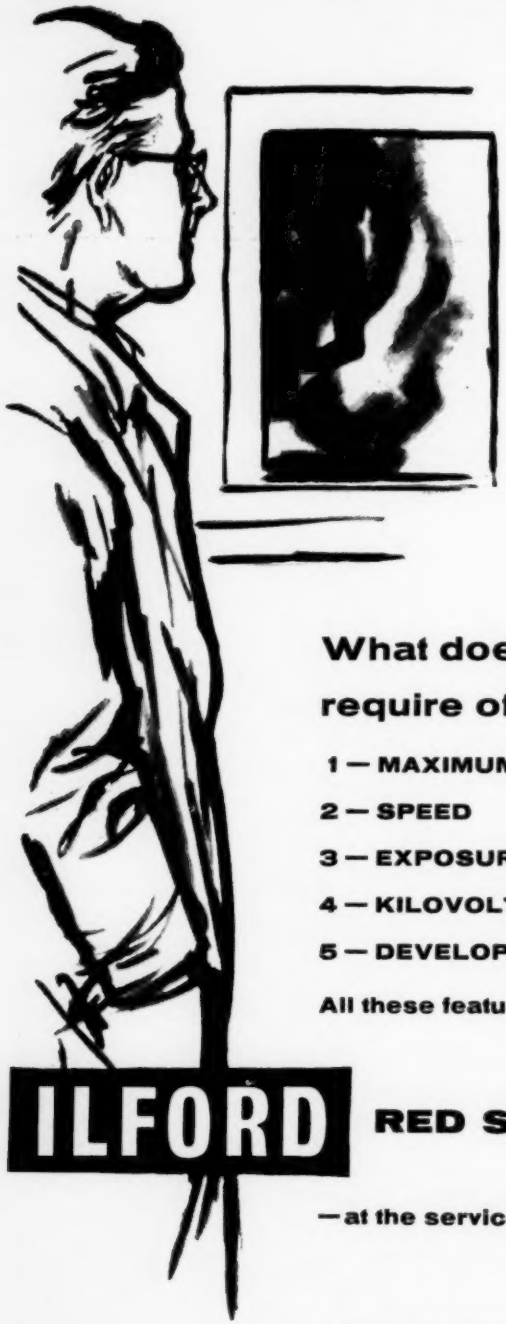

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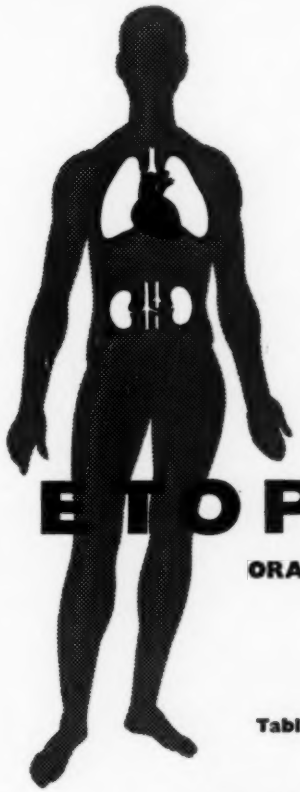

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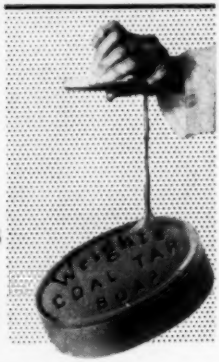

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References : B.M.J. *No. 5146, 22nd Aug. 1959*
LANCET, *9th May, 1959.*

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